THE ROLE OF CERVICAL LYMPH NODE METASTASES AND THEIR DISSECTION IN PAPILLARY THYROID CANCER EMPLOYING DIFFERENT SURGICAL APPROACHES WITH REGARDS TO THEIR LONG-TERM PROGNOSIS AND OUTCOMES

Mulla, Mubashir Ganie

Awarding institution:
King's College London

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Mr. Mubashir G Mulla

MB BS, MRCS, MMED

Department of Endocrine Surgery

King's College Hospital, London

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Summary of Thesis

Background

Papillary Thyroid Cancer (PTC) is a common endocrine cancer which metastases to the cervical lymph nodes (LN). The frequency of metastasis is poorly defined. The imaging modalities commonly employed to detect these metastases have limitations. The aim of this study was to define the extent of cervical LN metastases, the role of imaging in their detection and to determine long term outcomes.

Design and Methods

The study was designed in two parts.

A. Systematic reviews of incidence of cervical LN metastases in PTC and the use of imaging modalities in detection of these LN.

B. Retrospective Cohort Study of PTC patients: Data from three centres in London over the last 9 years was collected and analysed.

Results

I. Systematic reviews

A. **Central LN Dissection (LND)**: 21 studies provided data for 4188 patients. Among patients who underwent prophylactic central LND (pCLND), 772 had positive central LN (44.8 %).

B. **Lateral LND**: 19 studies provided data for 5587 patients. Out of 2048 patients who underwent pLLND, 1177 were found to have positive lateral LNs (57.5%).

C. Imaging of metastatic cervical LN

Ultrasound: The sensitivity to detect central and lateral cervical LN was 38.4% and 27.2% respectively.

Computerised Tomography: The sensitivity to detect central LN was 67%. For lateral LN none of the studies calculated the sensitivity accurately.

II. Results from the Cohort Study

44 patients were included in the analyses. 53.8% had positive LN when pLLND dissection was performed. Recurrence free survival between the two cohorts was not statistically significant. Overall survival was 100% for both groups.

Conclusions

Prophylactic LND yielded metastatic central and lateral LN in about half of all patients with PTC. Imaging modalities currently utilised for detection of metastatic central and lateral cervical LN have low sensitivities. In our cohort of patients, prophylactic lateral lymph node dissection did not show any significant difference in terms of long term outcomes.

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Abbreviations

ATA- American Thyroid Association

AUC- Area Under the Curve

CT- Computerised Tomography

18- FDG PET- fluoro- D-glucose Positron Emission Tomography

FNA- Fine Needle Aspiration

FN- False Negative

FP- False Positive

LN- Lymph Nodes

LND-Lymph Node Dissection

LNM- Lymph Node Metastases

MRI- Magnetic Resonance Imaging

NPV- Negative Predictive Value

PTC- Papillary Thyroid Carcinoma

pCLND- Prophylactic Central Lymph Node Dissection

pLLND- Prophylactic Lateral Lymph Node Dissection

PPV- Positive Predictive Value

RAI- Radio-iodine

ROC- Receiver Operating Characteristic

SLN- Sentinel Lymph Node

tCLND- Therapeutic Central Lymph Node Dissection

tLLND- Therapeutic Lateral Lymph Node Dissection

TN- True Negatives

TP- True Positives

TT- Total Thyroidectomy

USS- Ultrasound scan

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Statement of Originality

This research work produced in the thesis was undertaken entirely by the author Mubashir G Mulla at the Department of Endocrine Surgery, King's College Hospital.

Chapter 1

Thyroid Nodule and Carcinoma

1.1 Thyroid Nodule

Introduction

The most common presentation of thyroid cancer is a newly diagnosed thyroid nodule or increase in size of an existing nodule (Perros, Boelaert et al. 2014). Thyroid nodules are common clinical findings with a prevalence of 3-7% on palpation (Tunbridge, Evered et al. 1977). With increased use of high resolution ultrasound scans, the incidence is reported to be much higher in the region of 20-76% (Ezzat, Sarti et al. 1994). Clear majority of those presenting with a thyroid nodule however have benign disease. The clinical importance of thyroid nodules is primarily the need to exclude thyroid cancer which occurs in 7-15% of cases (Tan and Gharib 1997; Hegedus 2004).

The causes of thyroid nodules are listed in **Table 1.1 (Gharib, Papini et al. 2006)**

Table 1.1 Causes of Thyroid Nodules

- Benign nodular goitre
- Chronic lymphocytic thyroiditis
- Simple or haemorrhagic cysts
- Follicular adenomas
- Sub-acute thyroiditis
- Papillary carcinoma
- Follicular carcinoma
- Hurthle cell carcinoma
- Poorly differentiated carcinoma
- Medullary carcinoma
- Anaplastic carcinoma
- Primary thyroid lymphoma
- Sarcoma, teratoma, and miscellaneous tumors
- Metastatic tumours

1.1.1 Clinical evaluation and Investigation

Thyroid nodules are often accidental findings during clinical examination or on imaging for unrelated reasons (Gough, Scott-Coombes et al. 2008). Most patients with thyroid nodules do not have any symptoms. In symptomatic patients, a detailed history and examination will help guide further investigations. History should include a change in nodule size, rate of growth, previous head and neck irradiation and a family history of thyroid diseases (Yeung and Serpell 2008). Other associated symptoms include difficulty in swallowing or breathing which is suggestive of compressive effect from the thyroid swelling (Eng, Quraishi et al. 2010). Hoarse voice is a strong indication of recurrent laryngeal nerve involvement and malignancy (Ross 2003). Clinical examination of the neck should include palpation of the thyroid gland to determine the characteristics namely the size, consistency, mobility, single nodule or multinodular and for palpable cervical lymphadenopathy (Eng, Quraishi et al. 2010). Clinical features which are associated with increased probability of malignancy in a thyroid nodule include (Perros, Boelaert et al. 2014)-

- Age less than 20 or older than 60 years
- Firmness of the nodule on palpation
- Rapid growth
- Fixation to adjacent structures
- Vocal cord paralysis
- Regional lymphadenopathy
- History of neck irradiation
- Family history of thyroid cancer

According to British Thyroid Association (BTA), patients with a thyroid nodule associated with any of the following will need urgent investigation (Perros, Boelaert et al. 2014);

- Unexplained hoarseness or voice changes associated with a goitre
- Thyroid nodule in a child
- Cervical lymphadenopathy associated with a thyroid mass (usually deep cervical or supraclavicular region)

- A rapidly enlarging, painless, thyroid mass over a period of weeks (a rare presentation of thyroid cancer and usually associated with anaplastic thyroid cancer or thyroid lymphoma).

1.1.2 Biochemical Evaluation

Functional status of the thyroid gland should be assessed as part of the initial investigation of thyroid nodules. Tests include serum thyroid-stimulating hormone (TSH), free thyroxine (T4), and free tri-iodothyronine (T3). Serum Thyroglobulin (Tg) can be elevated in most thyroid diseases and is therefore not recommended as a routine initial assessment of thyroid nodules (Haugen, Alexander et al. 2016).
If the serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is hyperfunctioning (hot), isofunctioning (warm), or non-functioning (cold) (Gharib and Papini 2007).
Hyperthyroidism in the setting of thyroid nodules may suggest the presence of one or more hyper-functioning (autonomous) adenomas and the risk of malignancy in such nodules is less than 1% (Cases and Surks 2000). Since hyper-functioning nodules rarely harbour malignancy, no cytologic evaluation is necessary. If overt or subclinical hyperthyroidism is present, additional evaluation is required (Haugen, Alexander et al. 2016). A higher serum TSH level is associated with increased risk of malignancy in a thyroid nodule as well as more advanced stage thyroid cancer (Haymart, Repplinger et al. 2008). Patients with a nodule and normal thyroid function tests (euthyroid) may have thyroid cancer and should have further investigations (Perros, Boelaert et al. 2014).

Thyroid antibodies such as thyroid peroxidase and anti-thyroglobulin antibodies are found in most patients with Graves' disease or Hashimoto's thyroiditis. TSH receptor autoantibodies are detectable in majority of patients with Graves' disease.
In patients with a family history of Medullary Thyroid Carcinoma and Multiple Endocrine Neoplasia (MEN) type II, calcitonin levels are also performed as part of the initial investigation.

1.1.3 Imaging Modalities for Thyroid Nodule

Thyroid Scintigraphy

Thyroid Scintigraphy is a procedure producing images of the thyroid gland obtained within 15–30 min after intravenous injection of Tc-99m pertechnetate isotope or 3–24 hours after the oral ingestion of radioactive Iodine^{131}. It has been relied upon in the past to assist in risk stratification of nodules as being benign or malignant based on their ability to take up the isotope. Depending on the pattern of uptake, nodules are classified as hyper-functioning (hot), hypo-functioning (cold), or normal functioning (warm). Hot nodules are seen in about 5% of scans and are malignant in 5% of cases (Wong and Wheeler 2000). Approximately 80%–85% of nodules are cold and 10%–15% of these are malignant (Meier and Kaplan 2001).

Primary or secondary carcinomas of the thyroid almost invariably appear as nonfunctioning (cold) areas on the images (Mettler 2012), however most more than 90% of the 'cold' lesions are due to benign processes (eg. adenoma, thyroiditis, cyst etc). However, if a ‘cold’ nodule is found on thyroid scan, further investigation such as ultrasound and fine needle biopsy are recommended.

Ultrasound Scan (USS)

USS forms part of the initial investigation of thyroid nodule along with clinical examination and Fine Needle Aspiration Cytology (FNAC).

USS is readily available, non-invasive and an inexpensive investigation. All patients with thyroid nodule should undergo ultrasound evaluation of the nodule, thyroid gland, and cervical lymph nodes. It is helpful in identifying the nodules on which FNAC is necessary and also consistently increases the yield of diagnostic FNAC (Cesur, Corapcioglu et al. 2006; Hambly, Gonen et al. 2011).

USS helps to differentiate benign from malignant nodules. However, no single feature is diagnostic (Perros, Boelaert et al. 2014). USS features indicative of benign and malignant lesions are listed in Table 1.2.

Table 1.2 : USS features of benign and Malignant nodule (Perros, Boelaert et al. 2014)

US features indicative of benign nodule

- spongiform or honeycomb appearance (micro-cystic spaces with thin walls, comprising >50% of the nodule)
- purely cystic nodule and nodules with a cystic component containing colloid (hyper-echoic foci with a 'ring-down' sign)
- egg shell type calcification around the periphery of a nodule
- iso-echoic or (mildly) hyper-echoic in relation to the surrounding normal thyroid tissue and typically with a surrounding hypo-echoic halo
- peripheral vascularity on colour flow or power Doppler

US features indicative of malignant nodule

Papillary and Medullary cancers

- a solid hypo-echoic (i.e. hypo-echoic relative to the normal thyroid tissue) nodule, which may contain hyper-echoic foci (i.e. microcalcification)
- an irregular margin, intra nodular vascularity and absence of an associated halo
- a 'taller than wide' shape referring to Anterior/Posterior (AP > Transverse (TR) diameter when imaged in the axial plane. AP diameter >TR
- diameter increasing the likelihood of malignancy)
- an irregular or spiculated margin and a 'taller than wide' shape have both been shown to have good Positive Predictive Value for malignant
- nodules
- egg shell type calcification around the periphery of a nodule with a broken calcified rim where there is extension beyond the calcified rim of a
- hypo-echoic mass

Follicular lesions

- typically hyper-echoic and homogenous in echo texture with a well defined halo
- hypo-echogenicity and loss of the associated halo -associated with carcinoma

A graphic representation of the recognised signs that can be used to classify thyroid nodules is shown in Fig 1.1 (Perros, Boelaert et al. 2014). The description of the classification of thyroid nodules on ultrasound scan (U1-U5) is shown in Table 1.3 (Perros, Boelaert et al. 2014). As is evident from the table, it is used to differentiate between benign and malignant nodules. Such a classification system for the prediction of malignancy helps to determine whether a FNAC should be performed (Kim, Park et al. 2002; Moon, Jung et al. 2008).

Figure 1.1 Graphic features of thyroid nodules as seen on USS.

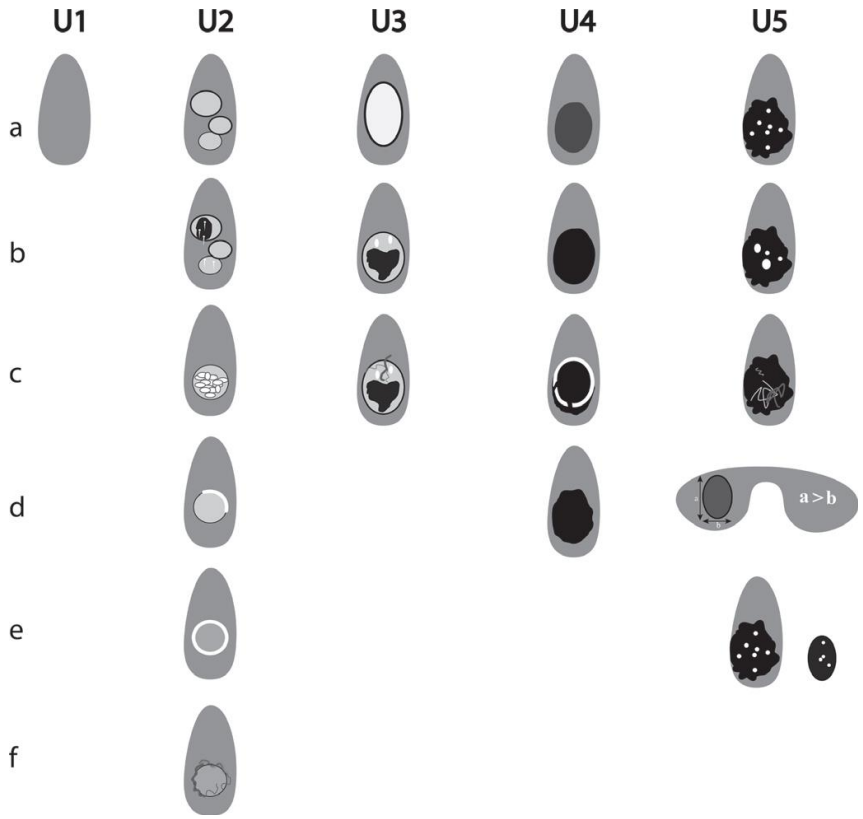


Table 1.3: Desciption of Ultrasound Scan classification of thyroid nodules

Ultrasound Category	Features
U1	**Normal**
U2	**Benign** (a) halo, iso-echoic / mildly hyper-echoic (b) cystic change +/- ring down sign (colloid) (c) micro- cystic / spongiform (d & e) peripheral egg shell calcification (f) peripheral vascularity.
U3	**Indeterminate/Equivocal** (a) homogenous, hyper-echoic (markedly), solid, halo (follicular lesion). (b) ? hypo-echoic, equivocal echogenic foci, cystic change (c) mixed/central vascularity.
U4	**Suspicious** (a) solid, hypo-echoic (cf thyroid) (b) solid, very hypo-echoic (cf strap muscle) (c) disrupted peripheral calcification, hypo-echoic (d) lobulated outline
U5	**Malignant** (a) solid, hypo-echoic, lobulated / irregular outline, micro-calcification (? Papillary carcinoma) (b) solid, hypo-echoic, lobulated/irregular outline, globular calcification (? Medullary carcinoma) (c) intra-nodular vascularity (d) shape (taller >wide) (AP>TR) (e) characteristic associated lymphadenopathy

1.1.4 Fine Needle Aspiration Cytology (FNAC)

FNAC forms part of the triple assessment of thyroid nodule. It is the procedure of choice in the workup of thyroid nodules (Cooper, Doherty et al. 2006). It is also a cost effective pre-operative investigation for thyroid nodules (Bajaj, De et al. 2006). It helps to diagnose a benign nodule and provide definite diagnosis for some thyroid malignancies enabling one stage therapeutic surgery (Perros, Boelaert et al. 2014). However, there are some limitations of FNAC as indicated below;

1. High rate of inadequate/unsatisfactory samples
2. Inability to distinguish between non-neoplastic, benign and malignant follicular lesions (Pauzar, Staklenac et al. 2010)
3. Difficulty in detecting follicular variant of papillary thyroid carcinoma (Chang, Lin et al. 2006).

USS guided FNAC samples have increased accuracy (Cai, Valiyaparambath et al. 2006; Nixon, Ganly et al. 2010) and reduced rates of unsatisfactory samples (Cesur, Corapcioglu et al. 2006). It is essential that adequate material is obtained for diagnosis and microscopy is performed by experienced pathologists (Porterfield, Grant et al. 2008). Aspiration should be ideally be performed by adequately trained personnel with expertise in thyroid disease (Perros, Boelaert et al. 2014). Reporting of the cytology samples in the United Kingdom is performed according to Royal College of Pathologists guidance using the Thy classification (Cross P 2016) as described in Table 1.4.

Table 1.4: Summary of Classification of thyroid nodules on cytology and recommended actions (Eng, Quraishi et al. 2010; Perros, Boelaert et al. 2014)

Diagnostic category	Description	Recommended action
Thy 1	Non-diagnostic, insufficient sample. Cyst containing colloid or histiocytes only, in the absence of epithelial cells	To repeat FNAC. Ultrasound guidance may help. If cyst aspirated to dryness with no residual swelling, clinical/ ultrasound follow-up alone may be sufficient.
Thy 2	Benign, non-neoplastic. Cyst containing benign epithelial cells.	Repeat FNAC in 3-6 months. Two non-neoplastic results 3-6 months apart should exclude neoplasia
Thy 3a	atypical features suspected	USS assessment+/- repeat FNA. MDT discussion
Thy3f	Follicular neoplasm or follicular variant of papillary thyroid carcinoma is suspected	Diagnostic Hemithyroidectomy
Thy 4	Suspicious of malignancy.	MDT discussion - surgical intervention, e.g. Total Thyroidectomy
Thy 5	Diagnostic of malignancy	MDT discussion - surgical intervention, e.g. Total Thyroidectomy

The categories can provide useful information of the likelihood of their malignant potential. As the Thy categories increases from 1-5, so does the malignant potential. In Thy 1, malignancy can be found in nodules in 4.5–8.5% of cases (Orija, Pineyro et al. 2007; Al Maqbali, Tedla et al. 2012). The risk is higher (14.3%) if the lesion is cystic

(Garcia-Pascual, Barahona et al. 2011). Thy 3 cases can have malignancy rate of 9.5-43% especially with suspicious USS features (Maia, Matos et al. 2011; Wang, Friedman et al. 2011). Thy 4 cytology is associated with malignant histology in about 68–70% (Wu, Jones et al. 2006) cases. The likelihood of a malignancy for Thy 5 is 100%, although rates of 98-99% have been reported (Jo, Stelow et al. 2010; Wang, Friedman et al. 2011).

Another method of thyroid nodule cytology classification is the Bethesda system described initially by National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference in 2007 (Crippa, Mazzucchelli et al. 2010). It is also recommended by the American Thyroid Association (ATA). The two systems have comparable categories as described in Table 1.5.

Table 1.5 Comparison of Bethesda categories and the BTA classification

Bethesda Diagnostic Category		**British Thyroid Association**	
I	Non-diagnostic or unsatisfactory	**Thy 1**	Non-diagnostic
II	Benign	**Thy 2**	Non-neoplastic
III	Atypia of undetermined significance or follicular lesion of undetermined significance	**Thy 3a**	Atypical features present
IV	Follicular neoplasm or suspicious of follicular neoplasm	**Thy 3f**	Follicular neoplasm suspected
V	Suspicious of Malignancy	**Thy 4**	Suspicious of Malignancy
VI	Malignant	**Thy 5**	Diagnostic of Malignancy

1.1.5 USS Elastography

Conventional USS is still the first line investigation in thyroid nodules but there has been considerable variation in its diagnostic performances (Park, Kim et al. 2009; Moon, Baek et al. 2011). Elastography is a dynamic technique that uses USS to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force (Rago, Santini et al. 2007). It is applied to study the hardness and elasticity of nodules to differentiate malignant from benign lesions (Cochlin, Ganatra et al. 2002).

Its clinical application in thyroid nodes was first reported by Rago et al. (Rago, Santini et al. 2007) using a five-point scale described originally by Ueno and colleagues (Ueno E 2004). A score of 1 is defined as elasticity in the whole nodule, 2 as elasticity in a large part of the nodule, 3 as elasticity only at the peripheral part of the nodule, 4 as no elasticity in the nodule, and 5 as no elasticity in the nodule and in the posterior shadowing (Rago, Santini et al. 2007) . Another scoring system was described by Asteria and colleagues (Asteria, Giovanardi et al. 2008). They defined a score of 1 as elasticity that is entirely soft in the nodule, 2 as mostly soft in the nodule, 3 as mostly hard in the nodule, and 4 as entirely hard in the nodule (Asteria, Giovanardi et al. 2008). Based on these scoring systems, sensitivity to detect thyroid malignancy has been found to be between 94-97% and specificity between 81-100% (Rago, Santini et al. 2007; Asteria, Giovanardi et al. 2008).

Moon and colleagues (Moon, Sung et al. 2012) evaluated the role of elastography as an adjunctive tool to conventional USS in 676 patients with 703 solid nodules. In their study, neither elastography nor the combination of elastography and gray-scale USS showed better performance for diagnosing thyroid cancers compared with conventional US. Elastography has shown to be a promising technique in breast (Lee, Chang et al. 2014) and liver imaging (Kim, Lee et al. 2013). Addition of elastography to conventional USS should improve the diagnostic performances, however the results are conflicting of its additional value in predicting thyroid malignancies (Bhatia, Tong et al. 2012; Kim, Kim et al. 2013; Russ, Royer et al. 2013). Therefore, the value of elastography in the routine in the assessment of thyroid nodules needs to be established.

1.1.6 Imaging Modalities in Thyroid Carcinoma

For any cancer, it is important to have accurate staging to plan treatment as it impacts on the long-term outcomes and survival. In PTC, the importance of a thorough preoperative evaluation and subsequent neck dissection to an appropriate extent during initial surgery has been emphasized in many studies (Chow, Law et al. 2003; Mazzaferri 2009).

Ultrasound Scan (USS)

The role of USS in triple assessment of thyroid nodules and the characteristic features seen on USS have been described in above chapter.

USS features of PTC include a solid hypoechoic nodule with a well or poorly defined margin and small foci of punctate calcification (Appetecchia and Solivetti 2006). PTC occasionally shows cyst formation as the dominant feature (Yuan, Chiou et al. 2006). Medullary carcinoma shows punctate calcification; calcification is however rare in follicular carcinoma. Anaplastic carcinomas are usually large necrotic tumours that extend outside the thyroid gland (Kebebew, Greenspan et al. 2005).

CT and MRI Scans

Computed tomography (CT) and Magnetic Resonance Imaging (MRI) are inferior and less sensitive to ultrasound in the investigation of thyroid cancer (Chaudhary and Bano 2012). Small tumours and thyroid nodules readily identified by ultrasound may be undetectable by these imaging modalities (King, Ahuja et al. 2000; Shetty, Maher et al. 2006). There are no definite CT features that distinguishes benign from malignant lesions and it underestimates nodularity (Shetty, Maher et al. 2006). When found on CT, punctate calcification or cystic components may be detected (Shetty, Maher et al. 2006), while on MRI the cystic components show a high T1 signal intensity.

The main role of CT and MRI is to demonstrate extra-thyroidal tumour extension, spread of disease into the mediastinum or retro-tracheal region and detecting pulmonary and hepatic metastasis which is essential in staging of the disease (Chaudhary and Bano 2012; Perros, Boelaert et al. 2014). CT and MRI are also

recommended to evaluate occult metastases in post-thyroidectomy cases with elevated serum thyroglobulin (Tg) levels and negative USS finding (Cooper, Doherty et al. 2009).

$^{131/123}$I whole body scan (WBS)

$^{131/123}$I whole body scan serves as an adjunct to clinical evaluation and serum Tg testing following thyroidectomy and ablative ^{131}I therapy (Taylor, Hyer et al. 2004) . It is used to detect residual loco-regional disease in the neck and distant metastases usually after surgery has been performed (King 2008). A positive diagnostic scan may demonstrate persistent disease following ablation (Grigsby, Baglan et al. 1999). In the UK, ^{131}I WBS has been used to assess the success of Radio-iodine Remnant Ablation (RRA) with stimulated thyroglobulin (Tg) (Perros, Boelaert et al. 2014). In recent years, stimulated Tg and specialised USS (Torlontano, Crocetti et al. 2006) has been favoured as a means of assessing RRA success without the need for diagnostic ^{131}I WBS (Schlumberger, Berg et al. 2004; Sherman 2013).

F-18 FDG PET/CT (Positron Emission Tomography/Computed Tomography)

^{18}FDG-PET (2-deoxy-2-_F-18_fluoro-D-glucose) is an integral part of investigation for many cancers such as lymphoma, melanoma, metastatic gastro-intestinal, lung, and head and neck cancer (Mosci and Iagaru 2011). However, it is not recommended as a routine investigation in the initial assessment of well differentiated thyroid cancer (Haugen, Alexander et al. 2016). Its main role is in investigation of persistent or recurrent disease. One scenario where its use is well established is in patients presenting with elevated Tg levels and negative radioactive iodine scan (Fletcher, Djulbegovic et al. 2008; Chaudhary and Bano 2012).

^{18}FDG-PET is useful in differentiating incidentaloma (focal uptake) from thyroiditis and hypothyroidism (diffuse uptake); and malignant thyroid which shows a very high FDG activity approaching 100% (de Geus-Oei, Pieters et al. 2006; Soto, Halperin et al. 2010). ^{18}FDG-PET has also been found to be the most accurate in detecting recurrent

or metastatic medullary thyroid carcinoma with an elevated calcitonin levels (Szakall, Esik et al. 2002; Iagaru, Masamed et al. 2007; Chaudhary and Bano 2012).

1.1.7 Imaging of Cervical Lymph Nodes

Ultrasound Scan (USS)

USS is commonly used and is the imaging modality of choice in the pre-operative evaluation of cervical Lymph Nodes (Watkinson, Franklyn et al. 2006). It is recommended by various organisations including the American Thyroid Association (Cooper, Doherty et al. 2009). The main current use of US is to identify the presence of suspicious LN to guide FNA which in turn will help to differentiate between benign and malignant LN.

Features which are suspicious of metastatic LN are (Kim, Park et al. 2008; Sugitani, Fujimoto et al. 2008) are as follows:

a) clear hypo-echoic or in-homogenous pattern

b) irregular cystic appearance

c) presence of internal micro-calcification and

d) rounded shape with increased antero-posterior diameter

However the US features of metastatic LN are not standardised (Kessler, Rappaport et al. 2003) and the accuracy of differentiation can be low (Rosario, de Faria et al. 2005). Ultrasound-guided biopsy improves diagnostic accuracy, however in patients especially with PTC multiple very small nodes are found and unless punctate calcification is identified, it can be difficult to establish a pre-operative diagnosis (King 2008).

CT and MRI scan

Computerised Tomography (CT) is also used in pre-operative evaluation of cervical LN although not routinely employed. However USS is considered better than CT to characterize features of metastatic LN as small as 5 mm in diameter due to its high-resolution images (Na, Choi et al. 2015).

Features which are suspicious of LN metastasis on CT are as follows (Som, Brandwein et al. 1994; Kim, Park et al. 2008)

a) cystic change

b) calcification

c) hyperenhancement

d) central necrosis

The following features seen on MRI are considered suspicious of metastatic disease (Gross, Weissman et al. 2001; Liu, Xun et al. 2014)

a) Long-diameter≥10 mm with high T2 weighted signal intensity

b) Short diameter

c) Central Necrosis or cystic degeneration

d) Enhancing lesions

e) Clustering

f) Fusion

A combination of USS, CT and MRI is advised in the assessment of thyroid cancer pre-operatively (Perros, Boelaert et al. 2014).

1.2 Thyroid Carcinoma

1.2.1 Introduction

Thyroid cancer is the most common malignancy of the endocrine system (Hundahl, Fleming et al. 1998). It accounts for about 1% of all cancers around the world with over 140,000 new cases every year (Parkin, Bray et al. 2005). It's incidence has continuously increased all over the world (Curado M. P 2007). In Great Britain, incidence rates have more than doubled from 1.5 to 3.1 per 100,000 over the last four decades (Compeau, Tyrwhitt et al. 2009). Increased incidence of thyroid cancer has been shown in certain regions of the pacific (Le Vu, de Vathaire et al. 2000; Truong, Rougier et al. 2007) and in the last few decades in industrialized nations like France (Reynolds, Weir et al. 2005; Davies and Welch 2006).

The exact reasons for the global rise of thyroid cancer remain unclear; there is an argument whether this is a true or an apparent increase. Most experts believe that the increased number of new cancers is due to the increased diagnostic intensity especially of small tumours (Davies and Welch 2006; Grodski, Brown et al. 2008). Incidental detection of thyroid tumours has also increased in recent years from increasing use of Doppler examination of the neck vessels and other imaging procedures like PET scans (Yun, Noh et al. 2010; Nilsson, Arnberg et al. 2011). There are others who believe that when improved detection is the only cause, the increase of small and early stage tumours should be accompanied by a progressive decline of larger and more advanced tumours (Pellegriti, Frasca et al. 2013). However this is not the case and the rise of thyroid cancer incidence whilst most prominent for small tumours, has occurred across all tumour sizes and stages, suggesting that increased detection is not the only cause (Enewold, Zhu et al. 2009; Rego-Iraeta, Perez-Mendez et al. 2009). Increased exposure to radiation is the most likely contributing factor for any true increase in the incidence but also other environmental carcinogens and lifestyle changes are a possibility (Pellegriti, Frasca et al. 2013). It is the fifth most common cancer in women (Jemal, Siegel et al. 2010); and in some countries like Italy, it is the second most common cancer in women below 45 years of age (Dal Maso, Lise et al. 2011).

1.2.2 Classification of Thyroid Cancer

I. Follicular Epithelial Cell Origin

A. Differentiated Thyroid Cancer

1. Papillary Thyroid Cancer (PTC)

a) Classic morphology

b) Encapsulated variant

c) Follicular variant

d) Aggressive variants

1. Diffuse sclerosing variant
2. Tall cell variant
3. Columnar Cell variant

2. Follicular Thyroid carcinoma (FTC)

a) Classic morphology ('follicular carcinoma')

-minimally invasive versus widely invasive

b) Hurthle Cell variant

- minimally invasive versus widely invasive

B) Poorly differentiated thyroid cancer (Insular Carcinoma)

C) Undifferentiated thyroid cancer (Anaplastic Carcinoma)

II. Parafollicular C-Cell origin

Medullary Thyroid Carcinoma (MTC)

III. Other Malignant neoplasm

-Lymphoma

-Metastatic tumours

1.2.3 Differentiated Thyroid Carcinoma

This includes **Papillary** and **Follicular Thyroid Carcinomas.** Papillary Thyroid Carcinoma (PTC) is the most common type of thyroid malignancy accounting for nearly 75% of all thyroid malignancies (Hundahl, Cady et al. 2000).

1.2.4 Risk Factors for Differentiated Thyroid Cancer

Radiation exposure

Exposure to radiation is a proven risk factor in the aetiology of papillary thyroid cancer (Hunt 2009). The thyroid gland is likely to be exposed to radiation more than other tissues because of its position in the body and its ability to concentrate iodine (Pellegriti, Frasca et al. 2013). In the past, thyroid carcinomas were more frequent in patients treated with low dose radiation for benign head and neck disease (DeGroot and Paloyan 1973). During the last quarter of a century, the individual radiation dose has doubled in developed countries like the USA (Mettler, Bhargavan et al. 2008). This has been attributed mainly due to medical diagnostic and therapeutic procedures (Mettler, Bhargavan et al. 2008). The increased use of CT scans in childhood has been attributed to a potential increase in thyroid cancer (Mazonakis, Tzedakis et al. 2007; Berrington de Gonzalez, Mahesh et al. 2009). The use of I^{131} either for diagnostic reasons or therapeutic purposes in hyperthyroidism is another source of thyroid irradiation and has shown to cause a small increase in thyroid cancer (Franklyn, Maisonneuve et al. 1998; Metso, Auvinen et al. 2007). Due to the increase in the use of radiotherapy for many cancers, survivors have been found to develop PTC in later life (Chow, Friedman et al. 2009).

After the nuclear bomb attacks in World War II, there have been reports of increased incidence of PTC in survivors (Wood, Tamagaki et al. 1969; Nakachi, Hayashi et al. 2008). Unusual thyroid tumours have also been reported in individuals living near areas near nuclear bomb test sites (Anspaugh, Ricker et al. 1990; Takahashi, Schoemaker et al. 2003). Similar reports of increased incidence of thyroid cancer

have been well documented after the Chernobyl nuclear disaster (Tronko, Bogdanova et al. 2010; Saenko, Ivanov et al. 2011).

Iodine Deficiency and Goitre

Thyroid stimulating hormone (TSH) is a major growth factor for thyroid follicular cells and iodine deficiency causes an increase level of this hormone. Some animal experiments have demonstrated an increase of thyroid cancer after prolonged iodine deficiency. However, this has not been demonstrated in humans residing in iodine deficient areas (Dal Maso, Bosetti et al. 2009). In iodine deficient areas, the over-all incidence of follicular carcinoma seems to be more than the papillary type (Feldt-Rasmussen 2001). This shift from a follicular to a papillary histotype may be due to the frequency of the BRAF(V600E) mutation, a typical molecular alteration in PTC (Pellegriti, Frasca et al. 2013).

Chronic iodine deficiency seems to be a risk factor for follicular thyroid cancer, and possibly anaplastic thyroid cancer (Besic, Hocevar et al. 2010). The major risk factor for goitre and nodularity is iodine deficiency, and both goitre and nodules are major risk factors for thyroid cancer in both men and women (Pellegriti, Frasca et al. 2013). One study reported a relative risk for thyroid cancer of 5.9 (95% CI 4.2–8.1) in individuals with a history of goitre and a much higher risk in those with a history of benign nodularity (Franceschi, Preston-Martin et al. 1999). Williams et.al have reported that dietary iodine concentrations influence the morphology of the papillary carcinomas (Williams, Abrosimov et al. 2008). They found that PTC amongst children in iodine deficient areas showed more aggressive and less differentiated morphological features than those from iodide-rich areas (Williams, Abrosimov et al. 2008).

Other Risk Factors

Other known risk factors for thyroid cancer are non-modifiable with patient age, sex, ethnicity and family history serving as the strongest predictors of risk (Kitahara and Sosa 2016). Women have approximately 3-4 times higher incidence of thyroid cancer than men, this ratio has remained constant over time and across countries (Kilfoy, Zheng et al. 2009). This difference is more pronounced for PTC compared to other

histological subtypes (Kilfoy, Zheng et al. 2009). A SEER (Surveillance, Epidemiology, and End Results) based study from the United States found the incidence of PTC to be highest in Asian females, while papillary and follicular thyroid cancer were the highest among White males (Aschebrook-Kilfoy, Kaplan et al. 2013).

Although vast majority of differentiated thyroid carcinomas are sporadic (Dotto and Nose 2008; Nose 2008), familial tumours may account for 5–15% of thyroid cancers (Nose 2011). They fall under a broad category named Familial Non-Medullary Thyroid Carcinomas (FNMTC) and are follicular cell derived neoplasms. They encompass a heterogeneous group of diseases including both syndromic-associated tumours and non-syndromic tumours based on clinic-pathologic findings (Nose 2008).

Dietetic factors interfering with thyroid hormone synthesis such as cruciferous vegetables could also affect thyroid cancer risk, however this possibility has never been demonstrated (Peterson, De et al. 2012). The evidences of a possible effect of food or environmental pollutants on thyroid cancer are weak and not confirmed.

1.2.5 Histopathology

1.2.5a Classical Papillary Thyroid Cancer

The gross appearance of PTC is variable. Papillary carcinomas often average 2–3 cms, although lesions may be quite large or commonly sub-centimetre in size (LiVolsi). The lesions are firm and usually white in colour. There may be extensive sclerosis making the lesion resemble a scar especially in small lesions. In addition, cyst formation may be observed. Rarely lesions may be almost completely cystic, making diagnosis difficult (Carcangiu, Zampi et al. 1985; Baloch Z 2002).

Microscopically papillary carcinomas share certain features (Figure 1.2). The neoplastic papillae contain a central core of fibro-vascular (occasionally just fibrous) tissue lined by one or occasionally several layers of cells with crowded oval nuclei (Vickery 1983; Carcangiu, Zampi et al. 1985; Baloch Z 2002). Cellular features include clear nuclei, nuclear grooves, and pseudo-nuclear inclusions. The tumours invade lymphatics leading to multifocal lesions and to regional node metastases. Venous

invasion rarely occurs and metastases outside the neck are unusual (5–7% of cases) (LiVolsi).

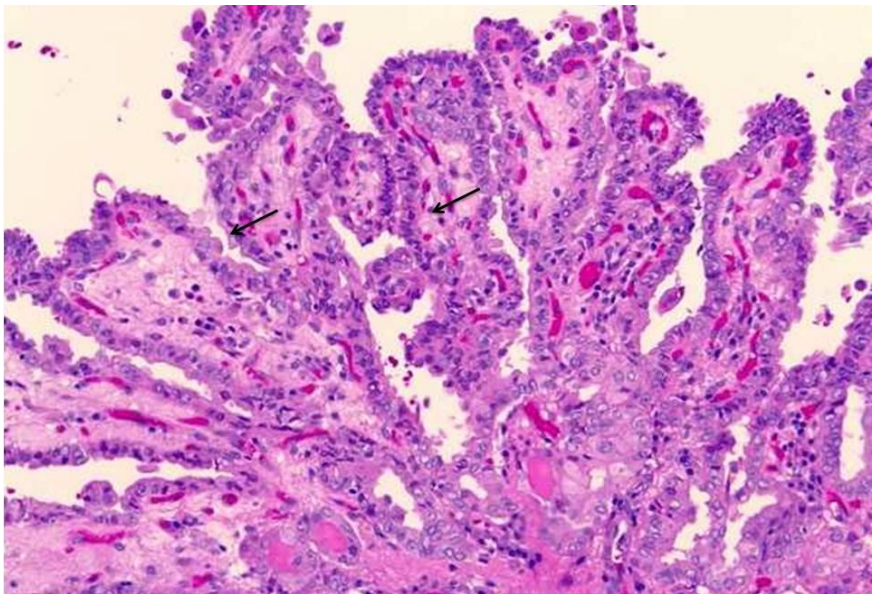


Figure 1.2 Papillary Thyroid Cancer-Finger like projections representing papillary growth pattern lined by neoplastic cells.

1.2.5b Histo-pathological variants

Micro-carcinomas

Commonly known as Papillary thyroid micro-carcinoma (PTMC), they are defined by the World Health Organisation (WHO) as PTC less than 1.0cm in largest dimension (DeLellis R 2004). In recent years, it is being diagnosed with increasing frequency. This has been attributed to the widespread use of USS and FNAC biopsy, as well as the improved resolution of ultrasonography (Noguchi, Yamashita et al. 2008; Grodski and Delbridge 2009).

Follicular variant

The follicular variant of PTC is the second most common subtype found in 9–22.5% of patients with PTC (Sebastian, Gonzalez et al. 2000; Passler, Prager et al. 2003). It has characteristic nuclear features of a typical PTC like nuclear clearing, grooves, and pseudo-inclusions in addition to a follicular growth pattern (Gupta, Ajise et al. 2012). These tumours can be a challenge for pathologists to diagnose accurately.

There are two further sub-types of the follicular variant of PTC, namely encapsulated and non-capsulated. Most of these are encapsulated tumors, which are difficult to distinguish from follicular adenomas (Gupta, Ajise et al. 2012). These subtypes appear to be distinct both clinically and genetically. A study showed that lymph node metastases were found to be 5% and 65% in encapsulated and non-encapsulated varieties respectively (Liu, Singh et al. 2006).

Aggressive variants

Tall Cell Variant

The tall-cell variant (TCV) is more aggressive than classical PTC. It was first described by Hawk and Hazard in 1976 (Hawk and Hazard 1976). It is an uncommon variant that is usually found in older patients and is associated with poor prognosis (Morris, Shaha et al. 2010). It is composed predominantly of tall cells with height at least twice width, eosinophilic cytoplasm, and basally oriented nuclei (Ghossein and Livolsi 2008). As a variant of PTC, the characteristic nuclear features of PTC are also present. A meta-analysis on prognostic outcomes found that TCV recurs with 4.50 times (CI: 2.90-6.99) greater odds than the classical variant and also had 14.28 (CI: 8.01-25.46) greater odds of disease-related mortality (Jalisi, Ainsworth et al. 2010). The same study also found that TCV had higher trends of lymph node and distant metastases and extra-thyroidal extension (Jalisi, Ainsworth et al. 2010).

Columnar cell variant

It is a rare variant of PTC accounting for 0.15% to 0.2% of all tumours; some authors group them together with TCV (Wenig, Thompson et al. 1998). In this variant, cells are tall with elongated hyperchromatic pseudostratified nuclei which differ from TCV cells in that they lack the cytologic nuclear features characteristic of TCV (Silver, Owen et al. 2011). Columnar cell variant are aggressive due to its rapid growth, high local recurrence rate, and frequent distant metastases (Silver, Owen et al. 2011).

Diffuse Sclerosing Variant

Diffuse sclerosing variant of PTC is characterized by dense sclerosis, patchy lymphocytic infiltration, and abundant psammoma bodies (Fujimoto, Obara et al. 1990). Both lobes of the thyroid are usually involved which often show a background of chronic lymphocytic thyroiditis. These variety is more common in younger patients between 15 and 30 years of age (Koo, Hong et al. 2009).

There are mixed reports regarding the aggressiveness and outcomes of this variant of PTC. Most authors have found high incidence of cervical metastasis, extracellular spread, local recurrence and distant metastases with decreased disease-free survival (Carcangiu and Bianchi 1989; Sywak, Pasieka et al. 2004; Falvo, Giacomelli et al. 2006). Some smaller series however have found no difference in the outcomes (Fujimoto, Obara et al. 1990; Albareda, Puig-Domingo et al. 1998).

Given the infiltrating nature of the disease and the propensity for lymph node metastases, more aggressive management of this variant with total thyroidectomy and appropriate lymphadenectomy is recommended for all patients (Silver, Owen et al. 2011).

Follicular Thyroid Carcinoma

Follicular Thyroid Carcinoma (FTC) is defined by WHO as a malignant epithelial tumour showing follicular cell differentiation and lacking the diagnostic nuclear features of papillary thyroid carcinoma (Sobrinho-Simoes, Eloy et al. 2011).

Follicular Thyroid Carcinomas are solid encapsulated tumours with gray to brown colour at the cut surface (Sobrinho-Simoes, Eloy et al. 2011). They usually occur as single tumours; multi-focality and recurrence in the residual parenchyma after treatment is uncommon. There are two sub-types of FTCs namely minimally and widely invasive. Macroscopically minimally invasive FTCs are indistinguishable from Follicular Adenomas (FA), except for capsular characteristics which tends to be thicker and more irregular in FTC than in FA (Rosai 2004). Widely invasive FTCs may occur as partially encapsulated tumours with extensive penetration of the capsule or as multi-nodular, bulking tumours without a capsule (Rosai 2004).

FTC often presents with more advanced disease and a higher incidence of distant metastases because of the propensity of vascular invasion (Lo, Chan et al. 2005). Lymph node metastasis is uncommon in FTC with an average incidence of about 10% (Thompson, Wieneke et al. 2001).

The prognosis of FTC depends on several factors: age of the patient, size and staging of the tumour, completeness of surgery and responsiveness to radioactive iodine. Age more than 45, male gender, extrathyroid invasion, bigger tumour size (>4cms), vascular invasion and presence of distant metastasis are recognized risk factors for poorer prognosis (Lang, Lo et al. 2007; Pisanu, Di Chiara et al. 2010).

Oncocytic/Hurthle Cell Variant

Hurthle cell carcinomas (HCC) account for about 5% of all well-differentiated carcinomas (Bhattacharyya 2003). Once considered to a subset of FTC, genomic dissection has revealed a unique class of thyroid malignancy distinct from papillary and follicular thyroid cancer (Ganly, Ricarte Filho et al. 2013). Because of the rarity, large scale data on this type of tumour is limited. These variants have the typical molecular features of their conventional counterparts of PTC and FTC, however they demonstrate a lesser ability to concentrate iodine and thus are less responsive to radioactive iodine therapy (Cannon 2011). HCC are commonly found in older patients, those who have undergone thyroid irradiation, long-standing nodular goiters, Graves' disease, and Chronic Lymphocytic Thyroiditis (Cannon 2011).

It can be difficult to determine if a Hurthle cell lesion is benign or malignant (Montone, Baloch et al. 2008). Although larger lesions have a higher incidence of malignancy, size in itself is not a criterion. The main criteria for malignancy include the presence of capsular and or vascular invasion (Montone, Baloch et al. 2008). Hurthle cell carcinomas do metastasize to the lymph nodes in about 3-25% (Guerrero, Suh et al. 2010); in addition they can spread to the lungs, liver and bone (Har-El, Hadar et al. 1986). There is conflicting evidence about the prognosis of HCC compared to the other types of differentiated thyroid carcinoma and FTC (Kushchayeva, Duh et al. 2008; Sugino, Kameyama et al. 2012).

1.2.6 Prognostic Factors for Papillary Thyroid Cancer

Age

It is a major prognostic factor in thyroid cancer and features in all prognostic scoring. Patients younger than 45 years of age do remarkably well compared with those older than 45 years (Shaha 2004). The mortality rates increases after 60 years of age (Mazzaferri and Jhiang 1994).

Gender

The importance of gender in PTC prognosis has been widely discussed in literature. Studies have shown that women have a higher incidence of thyroid nodules compared to men (Morganti, Ceda et al. 2005; Frates, Benson et al. 2006). However, the incidence of cancer in nodules tends to be higher in men (Machens, Hauptmann et al. 2006). Arguably women with thyroid cancer tend to have a better prognosis than men although the cause of this is not well established. One of the possible explanations for this could be because of differences in screening rates, such as the greater tendency of men to seek medical attention later than females (Toniato, Boschin et al. 2008).

Another possible explanation could be that papillary thyroid cancer tends to be diagnosed at an earlier age in females than in males (Lin, Hsieh et al. 2001). Male patients are higher risk of lymph node micro-metastasis (Teixeira, Teixeira et al. 2011). Studies have also shown a significant correlation between male gender and lung metastasis in papillary thyroid carcinoma presenting with bilateral lateral cervical lymph node metastasis (Lee, Lim et al. 2011).

Men tend to have higher recurrence rates and mortality (Mazzaferri and Jhiang 1994). This might be because men tend to have higher rates of extra-thyroidal invasion (51 vs 39%), greater likelihood of loco-regional lymph node involvement (40 vs 32%) and more than twice the rate of distant metastases (9 vs 4%) (Ries LAG 2003). A recent study found higher mortality and recurrence rates in males with PTC in TNM stages II to IV, suggesting the need for more aggressive surgical treatment

and postoperative radio-iodine therapy for this specific group of patients (Hsieh, Chen et al. 2012).

Tumour size

Size of the primary tumour features in most of the risk stratification systems for PTC namely AMES, MACIS, AGES etc. Long term survival and recurrence rates have been found to be worse for larger tumours. A large database study has shown ten-year recurrence rates increased with increasing tumour size: <1.0 cm 4.6%, 1.0- 1.9 cm 7.1%, 2.0 -2.9 cm 8.6%, 3.0-3.9 cm 11.6%, 4.0-8.0 cm 17.2%, and >8.0 cm 24.8% (*P* <0.0001) (Bilimoria, Bentrem et al. 2007). Similarly ten-year survival rates declined with increasing tumour size, but survival was statistically worse only for tumours larger than 4.0 cm (*P* <0.0001): <1.0 cm 98.0%, 1.0-1.9 cm 98.4%, 2.0-2.9 cm 98.5%, 3.0-3.9 cm 95.5%, 4.0-8.0 cm 90.5%, and >8.0 cm 81.3% (Bilimoria, Bentrem et al. 2007).

Other studies have also shown a linear correlation with the tumour size; there is a 0.4% long term mortality in tumours <1.5 cm increasing to 20% in tumours >4.5cm (Mazzaferri and Jhiang 1994). However, outcomes depend of variety of other factors including overall staging, type of surgical and adjuvant treatments.

Tumours < 1 cm i.e Papillary Thyroid Micro-carcinomas (PTMC) have a very good prognosis. From a recent database study looking at the outcomes of PTMC's, disease -specific survivals at 10 and 15 years were 99.5% and 99.3% respectively (Yu, Wan et al. 2011).

Histology

Histology of the tumour is an important determinant of long-term outcome. Differentiated Thyroid Cancer, including PTC has the most favourable survival rates, while MTC and ATC have been associated with significantly poorer outcomes (Hundahl, Fleming et al. 1998).

Among the histological subtypes of PTC, tall cell variant tends to present at a later stage and has a higher risk of loco-regional and distant relapse with worse overall survival compared to patients with classic PTC (Leung, Chow et al. 2008). In a large multicentre study looking at the PTC subtypes, follicular variant had the best

recurrence and mortality rates at 9.1% and 0.6% respectively. Classical PTC had recurrence and mortality rates of 16.1% and 2.5% whereas the tall cell variant had the worst figures with recurrence at 27.3% and mortality of 6.7% (Shi, Liu et al. 2016).

For FTC, the prognosis is generally good but the presence of metastatic disease makes it worse. A large study on FTC found that in patients without metastatic disease, 20-year disease-specific survival rates reached 80.2%, whereas for all FTC patients it was 73.7%. (Verburg, Mader et al. 2009). Another large study by Hundahl et al found a 10-year survival rate of 85% for FTC (Hundahl, Fleming et al. 1998).

For Medullary Thyroid Carcinoma (MTC), age and stage of disease at the time of diagnosis has been shown to be an important factor that influences prognosis (Wells, Asa et al. 2015). Studies have shown a worse disease free survival at five and ten years for patients <40 years as compared to >40 years of age (95 versus 65% and 75 versus 50%, respectively) (Kebebew, Ituarte et al. 2000).

The 10-year survival rates for patients with stages I, II, III, and IV MTC are 100, 93, 71, and 21% respectively (Wells, Asa et al. 2015).

Extra-thyroidal extension

Extension of thyroid cancer into the surrounding tissues, oesophagus and trachea is associated with a high-risk of loco-regional disease recurrence (Gemsenjager, Heitz et al. 2001). It is seen in as many of 30% of cases of PTC (Mazzaferri and Jhiang 1994). Even if the spread is microscopic and beyond the capsule, it is associated with a higher risk of recurrent disease (Jukkola, Bloigu et al. 2004) and greater likelihood of lymph node metastases (Lee, Lee et al. 2008). Studies have also shown that positive resection margins (R1) is associated with higher rates when compared to negative margins (R0) (Tuttle, Leboeuf et al. 2008; Hong, Ahn et al. 2012).

Lymph node metastases

LN metastases are more common in PTC when compared to other subtypes of thyroid cancer. The prevalence of lymph node metastases at the initial presentation has varied between studies. To some extent it depends on the imaging modalities used and the method employed in detection. The incidence of metastases ranges

from 20% to 90% with an average of 60% (Rotstein 2009). Other studies have reported similar percentages (Ito, Higashiyama et al. 2007; Jallon, Bonnet et al. 2009). In children, the numbers are even higher with up to 65% having central nodal disease at presentation (Kumar and Bal 2003).

The clinical importance of cervical LN metastases (CLNM) is however highly controversial. The key question whether the presence of CLNM, or their removal, affects long term survival remains largely unanswered. There are some studies which have found no difference in survival between patients with and without lymph node metastases (Hay, Bergstralh et al. 1993; Hughes, Shaha et al. 1996).

The reason for this is not fully understood. The speculation is the difference in the behaviour of tumour biology between thyroid and other solid cancers. Studies have shown that cancer cells disseminate relatively early in both lymphatic and blood vessels in a large proportion of adult solid cancers (Roberts, Hengesh et al. 1967; Griffiths, McKinna et al. 1973). These cells can be detected cytologically, yet their presence is not necessarily correlated with a poor outcome (Roberts, Hengesh et al. 1967). Whilst the spread to the lymph nodes may occur readily in thyroid cancer, this does not translate into distant metastasis readily unlike some other solid cancers (Cady 1984).

Other studies have found that their presence leads to an increased risk of recurrence (Ito, Higashiyama et al. 2007). A large cohort study has shown significantly reduced overall survival at 14 years in patients with lymph node metastasis compared to those with node negative disease (82 vs 79%, p-<0.05) (Podnos, Smith et al. 2005).

Distant metastases

Distant metastasis is seen in about 5-10% of patients with PTC and remains the main cause of mortality in patients with PTC (Benbassat, Mechlis-Frish et al. 2006; Durante, Haddy et al. 2006). The most common site is the lungs accounting for more than half of patients with distant metastases. 25% have bone involvement alone, 20% have both lung and bone involvement, and about 5% develop distant metastases at other sites (Lee and Soh ; Durante, Haddy et al. 2006).

1.2.7 Classification of Cervical Lymph Node Compartments

The most widely used classification is that proposed by the American Joint Committee on Cancer (AJCC) and the American Academy of Otolaryngology-Head and Neck Surgery first described by Robbins (Robbins, Clayman et al. 2002) displayed in **Table 1.6.** In addition to the above classification, cervical LN have also been classified based on axial imaging as described by Som and colleagues (**Table 1.7) (Som, Curtin et al. 2000).**

Table 1.6 Clinical classification of cervical LN (Robbins, Medina et al. 1991)

Levels	**Boundaries**	**Sub-classified and included Lymph nodes**
Level I	Anterior belly of the digastric muscle and the hyoid bone.	IA (Sub-mental).
	Between anterior and posterior bellies of digastric and the mandible.	IB (Sub-mandibular)-
Level II	Upper Jugular –from the carotid bifurcation or the hyoid bone to the base of the skull. Anterior boundary is the lateral border of sternohyoid; posterior boundary is the posterior border of sternocleidomastoid.	IIA- anterior to spinal accessory nerve.
		IIB- posterior to spinal accessory nerve.
Level III	Middle jugular- from the carotid bifurcation superiorly to the omohyoid muscle or cricothyroid notch inferiorly. Anterior boundary is the lateral border of sternohyoid, posterior boundary is the posterior border of sternocleidomastoid.	None.
Level IV	Lower Jugular- omohyoid muscle superiorly to the clavicle inferiorly. Anterior boundary is the lateral border of sternohyoid, posterior boundary is the posterior border of sternocleidomastoid.	None.
Level V-Posterior triangle group.	Posterior boundary is the anterior border of the trapezius muscle, anterior boundary is the posterior border of sternocleidomastoid	VA- those located above the horizontal plane defined by the inferior border of the cricoid

	(includes the supra-clavicular LN).	cartilage.
		VB- Below the horizontal plane defined by the inferior border of the cricoid cartilage.
Level VI Central Compartment.	Hyoid bone superiorly and the carotid arteries laterally, the inferior border has been variably defined as the sternal notch or the innominate (brachiocephalic) artery.	Pre-tracheal and para-tracheal nodes, the pre-cricoid (Delphian) node and the peri-thyroidal nodes, including nodes along the recurrent laryngeal nerves.
Level VII.	Superior mediastinal.	None.

Table 1.7 Imaging based classification of cervical LN (Som, Curtin et al. 2000)

Levels	**Boundaries**	**Sub-classified and included Lymph nodes**
Level I	Medial margins of the anterior bellies of the digastric muscles above the hyoid bone and below the mylohyoid muscle.	IA (Sub-mental)
	On each side of the neck, these nodes lie lateral to the level IA nodes and anterior to the back of each submandibular gland.	IB (Sub-mandibular)
Level II	These nodes extend from the skull base to the level of the bottom of the body of the hyoid bone. They are posterior to the back of the submandibular gland and anterior to the back of the sternocleidomastoid muscle.	II A-Level II nodes that lie either anterior, lateral, medial, or posterior to the internal jugular vein.
		II B- nodes that lie posterior to the internal jugular vein with a fat plane separating the nodes and the vein.
Level III	These nodes extend from the level of the bottom of the body of the hyoid bone to the level of the bottom of the cricoid arch. They lie anterior to the back of the sternocleidomastoid muscle.	
Level IV	These nodes extend from the level of the bottom of the cricoid arch to the level of the clavicle. They lie anterior to a line connecting the back of the	

	sternocleidomastoid muscle and the posterior-lateral margin of the anterior scalene muscle. They are also lateral to the carotid.	
Level V Posterior triangle group.	These nodes lie posterior to the back of the sternocleidomastoid muscle from the skull base to the level of the bottom of the cricoid arch. From the level of the bottom of the cricoid arch to the level of the clavicle as seen on each axial scan, they lie posterior to a line connecting the back of the sternocleidomastoid muscle and the posterior-lateral margin of the anterior scalene muscle. They also lie anterior to the anterior edge of the trapezius muscle.	V A- Extend from the skull base to the level of the bottom of the cricoid arch. They are posterior to the back of the sternocleidomastoid muscle.
		V B- extend from the level of the bottom of the cricoid arch to the level of the sternocleidomastoid muscle and the posterior-lateral margin of the anterior scalene muscle clavicle as seen on each axial scan.
Level VI Central Compartment.	These nodes lie between the carotid arteries from the level of the bottom of the body of the hyoid bone to the level of the top of the manubrium (previously known as the visceral nodes).	
Level VII	These nodes lie between the carotid arteries below the level of the top of the manubrium and above the level of the innominate vein (previously known as the superior mediastinal nodes).	
Supraclavicular.	These nodes lie at or caudal to the level of the clavicle as seen on each axial scan and lateral to the carotid artery on each side of the neck. They are also above and medial to the ribs.	
Retropharyngeal.	These nodes lie within 2 cm of the skull base and they are medial to the internal carotid arteries.	

1.2.8 Pattern of Metastases

The head and neck contains nearly two-fifths of the lymph nodes of the whole body, hence has a rich lymphatic network (Grodski, Cornford et al. 2007; Grubbs, Rich et al. 2008). The thyroid gland has an extensive lymphatic drainage which can follow a number of directions (Sakorafas, Sampanis et al. 2010). The risk of metastases to cervical LN in PTC has varied according to different studies. The incidence of LN

metastases has been reported to be between 20%-90% of cases (Rotstein 2009) . According to some reports the risk is greatest for lateral LN of levels II, III, and IV (Qubain, Nakano et al. 2002; Caron, Tan et al. 2006; Roh, Park et al. 2007). Overall central LN are more commonly involved and usually before lateral LN involvement (Goropoulos, Karamoshos et al. 2004). Bilateral central LN metastases is reported anywhere between 30-46% of patients (Noguchi, Kumaki et al. 1990; Machens, Hinze et al. 2002; Sadowski, Snyder et al. 2009). Other reports have suggested the ipsi-lateral central neck as the most common site of metastatic PTC. In about 20% of patients lateral LN are involved in isolation without any central LN involvement. They are also known as 'skip metastases'(Machens, Holzhausen et al. 2004).

Micro-Metastasis

It is defined as histological presence of metastatic deposits <2mm in diameter in a lymph node (Sakorafas, Sampanis et al. 2010) . The incidence varies according to the technique used to identify them. The incidence rates described in literature has varied between 50-66% (Qubain, Nakano et al. 2002; Cranshaw and Carnaille 2008).

1.2.9 Cervical Lymph Node Dissection

Cervical LND in PTC has evolved from radical surgery to more refined procedures with fewer complications. It is important to understand some of the surgical procedures that are practised. A summary of individual procedures is described below.

Radical Neck Dissection

This procedure was initially described in 1906 by George Crile (Soto-Ruiz and Varon 2009). This involves removal of all the lymph nodes in the neck along with three important anatomic structures namely the sternocleidomastoid muscle, the internal jugular vein and the spinal accessory nerve. This has major side effects including dysmorphy and shoulder dysfunction due to sacrifice of the spinal accessory nerve.

Vagus nerve injuries can occur resulting in significant dysphonia from ipsilateral vocal cord paralysis and dysphagia with pooling of secretions from pharyngeal paralysis.

Extended Radical Neck Dissection

In this, additional lymph node groups or non-lymphatic structures relative to the radical neck dissection are removed. Other LN groups may include superior mediastinal, retropharyngeal, peri-pharyngeal, post-auricular etc. Other non-lymphatic structure may include vagus nerve, hypoglossal nerve or external carotid artery. It is a more aggressive procedure than radical neck dissection.

Modified Radical Neck Dissection

First described in 1962 by Oswaldo Suarez, an Argentinian surgeon (Byers 1991) this procedure has gained popularity in Europe and in the United States of America. Here, dissection of Levels II-V cervical LN is done with sparing of the following structures: sternocleidomastoid muscle, internal jugular vein or spinal accessory nerve (CN XII) (Sitges-Serra, Lorente et al. 2013). Depending on which non-lymphatic structure is preserved, MRND is further subdivided into type I (preservation of the spinal accessory nerve), type II (preservation of the spinal accessory nerve and internal jugular vein), and type III (preservation of the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle) (Sakorafas, Sampanis et al. 2010).

Selective Neck Dissection

This involves preservation of one or more lymph node groups routinely removed in the radical neck dissection. The procedures are based on a 'compartment-oriented' dissection of LN. For example the central compartment LN dissection would involve removal of LN in level VI with preservation of the recurrent laryngeal nerve and at least one parathyroid gland.

Berry Picking

In this procedure, only suspicious and enlarged lymph nodes are removed. This type of surgery cannot achieve complete removal of metastatic disease and results in a

high incidence of recurrent disease requiring further surgery (Musacchio, Kim et al. 2003). The incidence of recurrences after this procedure has been reported to be as high as 86% (Davidson, Park et al. 2008). Hence this procedure is now of historical importance only.

1.2.10 Terminology of Neck Dissection

Central lymph node dissection is the removal of the level VI LN that lies in a central position in the neck. Level VI LNs includes pre-tracheal and para-tracheal nodes, the pre-cricoid (Delphian) node and the peri-thyroidal nodes including nodes along the recurrent laryngeal nerves (White, Gauger et al. 2007; Carty, Cooper et al. 2009). Lateral lymph node dissection (lateral LND) is defined as removal of the jugular lymph nodes corresponding to lymph nodes in level II-IV.(Robbins, Shaha et al. 2008; Cooper, Doherty et al. 2009).

There is now a consensus amongst leading endocrine organisations namely ATA (American Thyroid Association), AAES (American Association of Endocrine Surgeons) and AAO (American Academy of Otolaryngology) regarding the terminology used for neck dissection in thyroid cancer.

A 'therapeutic compartment neck dissection' also known as 'selective' implies that nodal metastasis is apparent clinically (preoperatively or intra-operatively) or by imaging (Carty, Cooper et al. 2009). In this all apparent LN, fatty tissue and fascia are removed from an anatomically defined compartment.

A 'prophylactic', also known as 'elective' compartment dissection implies nodal metastases are not detected clinically or by imaging pre-operatively (Carty, Cooper et al. 2009). This means removal of all lymph nodes from an anatomically defined compartment as part of the surgical procedure.

1.2.11 Staging of Papillary Thyroid Cancer

The most widely used and accepted staging of PTC is the TNM classification provided by the Union for International Cancer Control (UICC) and used by American Joint Committee on Cancer (AJCC) as shown in Table 1.8.

Table1.8 Staging of Papillary Thyroid Cancer (Edge SB 2010)

T- Primary tumour	
Tx	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
T1 <2 cm or less, limited to thyroid. T1a <1cm. T1b >1 cm but < 2cm.	
T2	>2 cm but <4 cm, limited to thyroid.
T3	> 4 cm, limited to thyroid or any tumour with minimal extra-thyroidal extension.
T4a: Extends beyond thyroid capsule and invades the following- subcutaneous soft tissues, larynx, trachea, oesophagus and recurrent laryngeal nerve. T4b Invades prevertebral fascia, mediastinal vessels or encases carotid artery.	
N- Regional Lymph Nodes.	
Nx	Regional LN cannot be assessed.
N0	No regional LN metastases.
N1	Regional LN metastases.
N1a	Metastases in Level VI.
N1b	Metastases in other unilateral, bilateral or contralateral cervical LN (Levels I, II, III, IV or VI).
M- Distant Metastasis.	
M0	No distant Metastases.
M1	Distant Metastases.

Once the T, N and M values are determined, grouping from I to IV is done as shown in Table 1.9.

Table 1.9 Group Staging- Papillary Thyroid Cancer

Under 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
45 years and older			
Stage I	T1a, T1b	N0	M0
Stage II	T2	N0	M0
Stage III T3 N0 M0 T-3 N1a M0			
Stage IVA T-3 N1b M0 T4a N0 M0			
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

As is evident from the Table 1.9, thyroid cancers are grouped in stages in a way that also considers the subtype of cancer and the patient's age. There are several systems which aim to stratify thyroid cancer patients according to risks to predict the treatment and outcomes. The most commonly used in PTC is the MACIS system (Table 1.10).

Table 1.10 Risk Stratification systems for Differentiated Thyroid cancer (Sakorafas, Sampanis et al. 2010)

AGES	AMES	MACIS	DAMES	GAMES	TNM/UICC
Age Metastases Extent Size	Age Metastases Extent Size	Metastases Age Completeness of Surgery Invasion Size	Diploid Age Metastases Extent Size	Grade Age Metastases Extent Size	Tumour size Nodal status Metastases

1.3 Treatment of Differentiated Thyroid Carcinoma

The pre-operative assessment and imaging methodology employed in the evaluation of thyroid cancer has been discussed in the previous chapters.

The general principles and guidelines for surgery in thyroid cancer are described below. The terminology related to thyroid cancer surgery as recommended by British Thyroid Association is described in Table 1.11 (Perros, Boelaert et al. 2014)

Table 1.11 Recommended terminologies for Thyroid Cancer

Procedure	Definition
Hemi-thyroidectomy	Complete removal of one thyroid lobe including the isthmus.
Near-total lobectomy	Total lobectomy leaving behind only the smallest amount of thyroid tissue (significantly less than 1 g) to protect the recurrent laryngeal nerves.
Near-total thyroidectomy	Complete removal of one thyroid lobe (lobectomy) with a near-total lobectomy on the contralateral side or a bilateral near-total procedure. This should be clearly defined in the operation note.
Total thyroidectomy	Removal of both thyroid lobes, isthmus and pyramidal lobe.

1.3.1 Surgery for Papillary Thyroid Cancer

The guidelines for the treatment of PTC from well renowned endocrine organisations are summarised in Table 1.12.

Table 1.12 Guidelines for Thyroid Surgery in Papillary Thyroid Cancer

	AACE/AAES (2001)	**BTA (2014)**	**ATA (2009)**	**NCCN (2008)**
Extent of Thyoidectomy Total or near total	High-risk cancer Ex (+) N (+) M (+) Bilateral nodularity Bilateral cancer	T >1 cm Ex (+) N (+) Multiple lesions Radiation history Family history	Age ≥ 45 T >1–1.5 cm N (+) M (+) Bilateral nodularity Radiation history Family history	Age <15 or >45 T >4 cm Ex (+) N (+) M (+) Bilateral nodularity Radiation history Aggressive variant
Lobectomy (+isthmusectomy)	T ≤1 cm Ex0 N0 M0	T ≤1 cm N0	Other than the Above	Other than the Above
Lymph node dissection **Central compartment** **Lateral compartment**	N (+) N (+)	N (+) or T >4cm N (+)	N (+) or T3 and T4 N (+)	N (+) N (+)

AACE-American Association of Clinical Endocrinologists

AAES- American Association of Endocrine Surgeons

BTA- British Thyroid Association (Perros, Boelaert et al. 2014)

ATA- American Thyroid Association (Cooper, Doherty et al. 2009)

NCCN- National Comprehensive Cancer Network

Ex- Extension of cancer beyond thyroid capsule

N (+) - Metastatic Lymph node on imaging

BTA recommends total thyroidectomy for large tumours or tumours of any size with additional risk factors. This has shown to be associated with fewer recurrences and better survival (Bilimoria, Bentrem et al. 2007; Pelizzo, Boschin et al. 2007).

According to ATA, patients with thyroid cancer >4 cm, or with gross extrathyroidal extension or clinically apparent metastatic disease to nodes or distant sites, the initial surgical procedure should include a near-total or total thyroidectomy (Haugen, Alexander et al. 2016).
For patients with tumours 4 cm or smaller and no risk factors, hemi-thyroidectomy without radioiodine remnant ablation (RRA) is reported to have an equally favourable outcome to total thyroidectomy (Nixon, Ganly et al. 2012; Matsuzu, Sugino et al. 2014).

1.3.2 Central Lymph Node Dissection

Guidelines from renowned endocrine associations regarding central LN dissection are tabulated in Table 1.12.
ATA recommendation is 'therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central or lateral neck lymph nodes' (Cooper, Doherty et al. 2009). 'pCLND (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumours (T3 or T4)'(Cooper, Doherty et al. 2009). The recommendation has 'B' and 'C' respectively which implies the strength is limited by the number, quality, or consistency of the individual studies or is based on expert opinion (Cooper, Doherty et al. 2009).

British Thyroid Association (BTA) guidelines do not recommend prophylactic central neck LN dissection for patients without clinical or radiological evidence of lymph node involvement, who have all of the following characteristics: classical type PTC, <45 years, unifocal tumour, ≤4 cm, no extra-thyroidal extension on US (Perros, Boelaert et al. 2014) .
The evidence is based on databases and retrospective cohort studies and hence not of the highest level (Costa, Giugliano et al. 2009; Moo, McGill et al. 2010; Moreno, Edeiken-Monroe et al. 2012; Barczynski, Konturek et al. 2013). For patients deemed to be high risk based on one or more of the following (adverse histological sub type, age ≥ 45 years, multifocal, tumours greater than 4 cm in diameter, extra-thyroidal

extension), the recommendation is ‘personalised Decision Making’. The level of evidence is described by BTA is ‘4,D’ which is again based on cohort studies. ‘Personalised Decision making’ involves multidisciplinary team meeting, expert opinion and available expertise locally (Perros, Boelaert et al. 2014).
Guidelines from the Japan Society of Thyroid Surgeons (JSTS) however recommend prophylactic central LND at initial surgery because reoperation for recurrence to this compartment may induce severe complications-‘recommendation rating= B’(Takami, Ito et al. 2011)

1.3.3 Lateral Lymph Node Dissection

ATA recommends therapeutic lateral LND for (Cooper, Doherty et al. 2009) biopsy proven metastatic lateral cervical lymphadenopathy. This recommendation has a ‘B’ rating according to ATA guidelines and relies on the detection of cervical LN on US. (Cooper, Doherty et al. 2009). As highlighted in our previous literature review, US has poor sensitivity and hence cannot be relied upon for staging PTC tumours (Mulla M 2012).
British Thyroid Association in its guidelines concludes that pLLND in patients without central LN metastases is not recommended (Perros, Boelaert et al. 2014). For patients with central LN metastases, the recommendation for pLLND is ‘personalised decision making’ (evidence Level ‘4D’) which is based on multidisciplinary team meeting, expert opinion and available expertise (Perros, Boelaert et al. 2014).
Guidelines from the Japanese Society of Thyroid Surgeons (JSTS) regarding the role of prophylactic lateral LND remains undetermined. However JSTS guidelines recognises the significance of pLLND in reducing recurrences (Ito Y 2010).

1.3.4 Treatment of Follicular Thyroid Carcinoma

FNAC cannot distinguish follicular adenoma or benign hyperplastic nodules from carcinoma. Follicular cytology (Thy3) usually mandates at least a diagnostic hemi-thyroidectomy (Perros, Boelaert et al. 2014). If definitive histology reveals a follicular adenoma or a hyperplastic nodule, no further treatment is required.

Patients with tumours ≤4 cm, in the absence of other adverse risk factors appear to have an excellent prognosis (Sugino, Kameyama et al. 2012; Goffredo, Cheung et al. 2013). BTA recommends hemi-thyroidectomy for these patients (Perros, Boelaert et al. 2014).

Patients with follicular tumours >4 cm appear to have worse prognosis (D'Avanzo, Treseler et al. 2004; Mete and Asa 2011) and should be treated with total thyroidectomy (Perros, Boelaert et al. 2014).

Patients with tumours >1–≤4 cm and adverse risk factors (age >45 years, widely invasive, lymph node/distant metastases, angioinvasion) should be treated with total thyroidectomy (Perros, Boelaert et al. 2014) .

1.3.5 Treatment of Hurthle Cell Carcinoma

Recommendations from British Thyroid Association (BTA) on the surgical treatment of HCC are as follows **(Perros, Boelaert et al. 2014)**

- In patients with tumour less than 1 cm hemi- thyroidectomy or total thyroidectomy is recommended.
- For carcinomas > 1 cm, total thyroidectomy is recommended
- Therapeutic lymph node dissection is advocated in patients with clinical or radiological evidence of lymph node involvement and confirmed metastasis.
- Evidence for prophylactic neck dissection is unclear.

1.3.6 Medullary Thyroid Carcinoma

Medullary thyroid cancer (MTC) accounts for nearly 5%–10% of all thyroid cancers (Sippel, Kunnimalaiyaan et al. 2008). It is a malignancy of the parafollicular 'C' cells of the thyroid. The C cells originate from the embryonic neural crest, hence MTC's often have the clinical and histological features of other neuro-endocrine tumours. The C cells secrete a variety of peptides and hormones with calcitonin being the most common. Serum calcitonin levels are elevated in patients with MTC and can be used to confirm the diagnosis as well as for follow-up of patients.

Most medullary thyroid carcinomas are sporadic, however about 25 percent are familial and form part of the Multiple Endocrine Neoplasia type 2 (MEN2) syndrome.

Their clinical course varies from an extremely indolent tumour to an aggressive variant that is associated with a high mortality rate.

Sporadic MTC's- They form nearly 75% of all cases of the disease. The typical age of presentation is in the fourth and sixth decades of life (Leboulleux, Baudin et al. 2004). The most common presentation is that of a solitary thyroid nodule which occurs in 75-95% of patients (Dottorini, Assi et al. 1996; Kebebew, Ituarte et al. 2000).

In most patients with MTC, metastasis has already occurred at the time of diagnosis. About 70% of patients have cervical metastases and 10% have distant metastases (Moley 2010). Central and lateral compartment lymph node metastases are present in 86% and 93% of patients with T4 tumours respectively (Machens, Hinze et al. 2002). Nodal metastases are reported to be more common in patients with multifocal disease (Machens, Hauptmann et al. 2007). Site of distant metastases are often the liver, lung, bones and less commonly to the brain and skin.

Hereditary or Familial MTC

As previously mentioned majority of MTC's are sporadic but about 20-25% are familial and form part of the MEN 2 syndrome (Multiple Endocrine Neoplasia). MEN2 is sub-classified into two distinct syndromes namely MEN2A and MEN2B) each of which is transmitted in an autosomal dominant pattern and associated with MTC. MEN2A is more common accounting for about 75% cases (Sippel, Kunnimalaiyaan et al. 2008). MEN2A, is associated with MTC, pheochromocytoma, and primary parathyroid hyperplasia. These tumours are typically bilateral and multicentric, age of presentation is variable but it is usually in early adulthood. Pheochromocytomas are seen in up to 50% of cases and can be screened for using either plasma metanephrines or 24-hour urine collections for catecholamines and metanephrines (Sippel, Kunnimalaiyaan et al. 2008). Screening for hyperparathyroidism can be performed with serum calcium and parathyroid hormone levels. Some other variants of MEN2A are also associated with cutaneous lichen amyloidosis or Hirschsprung's disease.

In MEN2B, there is similar inherited predisposition to MTC and pheochromocytoma as MEN2A, but does not include hyperparathyroidism. The tumour develops at an earlier age and has an aggressive course than in MEN2A. A characteristic feature of MEN-2B is the development of diffuse ganglioneuromas of the lips, tongues, eyelids, and gastrointestinal tract. These patients have a characteristic appearance, including a Marfanoid habitus, everted eyelids, and thick lips (Sippel, Kunnimalaiyaan et al. 2008).

Treatment of Medullary Thyroid Carcinoma

Unlike most other thyroid cancers, medullary thyroid cancer does not absorb RAI and therefore the best chance of curing a patient is completely removing the cancer at the first operation.

A summary of recommendations provided by British Thyroid association recommendation (BTA) (Perros, Boelaert et al. 2014) is as follows-

- Minimum of Total thyroidectomy and central LN dissection for established MTC.
- Patients with clinical or radiologically involved lymph nodes in the lateral compartment, patients should undergo selective lateral neck dissection of levels IIa–Vb in addition to total thyroidectomy and central lymph node dissection.
- Ipsilateral prophylactic lateral neck dissection is recommended in the presence of central compartment node metastases on the basis that the risk of lateral node involvement is at least 70%.
- About 35% patients with central compartment node metastases will have contralateral lateral compartment node metastases (Machens, Hauptmann et al. 2008). Studies have shown that bilateral lateral neck dissection in patients will achieve biochemical cure in 50% of patients (Machens and Dralle 2010). Although this will reduce calcitonin levels, its impact on survival is less certain. Therefore, prophylactic bilateral lateral compartment node dissection in the presence of central compartment node metastases is unclear.

- Children with MEN2B should undergo prophylactic thyroidectomy preferably within the first 6 months but within the first year of life (Leboulleux, Travagli et al. 2002; Brauckhoff, Machens et al. 2014)
- Children with MEN 2A should undergo thyroidectomy before the age of 5 years (Rohmer, Vidal-Trecan et al. 2011)
- Prophylactic lymph node dissection at the time of thyroidectomy should be considered in gene carriers based upon the basal calcitonin level.

Routine adjuvant external beam radiotherapy EBRT should be considered only once optimal surgery has been performed and if there is significant risk of local recurrence (Wilson, Millar et al. 2004)

1.3.7 Radioiodine Remnant ablation (RRA) for Differentiated Thyroid cancer

Also known as RRA, it is used as an adjunct to near total or total thyroidectomy in differentiated thyroid cancer (Perros, Boelaert et al. 2014). Iodine is concentrated by differentiated thyroid cancers but not by poorly differentiated carcinoma, medullary carcinoma, lymphomas and anaplastic carcinomas (Carballo and Quiros 2012). Hence these cancers which do not concentrate iodine are not candidates for Radio-iodine treatment (Carballo and Quiros 2012). After surgery for Differentiated Thyroid Cancer (DTC), some ^{131}I uptake is usually demonstrable in the thyroid bed. ^{131}I-induced destruction of this residual thyroid tissue is known as 'radioiodine remnant ablation' (RRA) (Perros, Boelaert et al. 2014).

Mechanism of Radio- Iodine Treatment

Radioiodine (RAI) is taken up and concentrated in thyroid follicular cells via a membrane called sodium-iodide transporter (Carballo and Quiros 2012) . Thyroid Stimulating Hormone (TSH) stimulates thyroid tissue and cancer cells to take up radioactive iodine. RAI therapy is most effective when circulating levels of TSH or

thyrotropin are high in blood. The most effective form of iodine isotopes used in the treatment for papillary thyroid cancer is I-131 (Silberstein 2012).

Optimisation of patients for RRA

-All patients should have undergone total thyroidectomy before administration of radio-iodine therapy. It has been shown that complete surgical removal of normal and pathologic thyroid tissue increases the efficacy of RAI treatment in destroying metastatic disease (Sakorafas, Sampanis et al. 2010). RAI treatment can be inefficient in tumours without radio-iodine uptake in 25-30% of cases (Jallon, Bonnet et al. 2009).
-Exogenous Iodine: Radio-iodine uptake is suppressed by increased endogenous stores or exogenous iodide. Exposure to iodinated intravenous contrast and treatment with drugs like amiodarone which is rich in iodine content may compromise the efficacy of radio-iodine (Perros, Boelaert et al. 2014). Generally, a low iodine diet two weeks prior to RRA is advised.

1.3.8 TSH stimulation with recombinant human TSH (rhTSH) or Thyroid Hormone Withdrawal (THW)

For ablative RAI treatment to be most effective, high TSH levels are required to maximise uptake by thyroid remnants or residual tumour cells (Reiners, Dietlein et al. 2008). This can be achieved by two different methods.
TSH can be stimulated exogenously by injection of rhTSH. Recombinant human TSH is a synthetic drug that is used to provide TSH stimulation without withdrawal of thyroid hormone and the associated symptoms and morbidity (Carballo and Quiros 2012). Alternatively, TSH can be stimulated endogenously by withholding thyroid hormone (T4) approximately 3 weeks after thyroidectomy (Serhal, Nasrallah et al. 2004). This is termed as 'Thyroid Hormone Withdrawal' (THW). This can cause hypothyroidism and the symptoms associated with it. Randomised trials have shown that RAI therapy is equally effective after rhTSH or THW for selected patients with DTC (Mallick, Harmer et al. 2012; Schlumberger, Catargi et al. 2012).

Recombinant TSH is the recommended method of preparation for RRA in patients with T1 to T3 tumours with no lymph node or distant metastases (Perros, Boelaert et al. 2014). It is not currently used for patients with high risk of recurrence, or for the treatment of recurrent or metastatic DTC (Perros, Boelaert et al. 2014).

1.3.9 Indications for RRA

There is no clear evidence that all patients will benefit from RRA. In a significant group, the evidence is inadequate and conflicting. Therefore clear recommendation cannot be made (Perros, Boelaert et al. 2014) and are not available (Haugen 2004; Hackshaw, Harmer et al. 2007). For these reasons, RRA patients can be classified into three categories: (a) definite indications for RRA (b) uncertain indications for RRA (c) no indication for RRA as in Table 1.13.

Table 1.13 Indications of RRA (Perros, Boelaert et al. 2014)

Definite Indications	No Indications	Uncertain Indications
Any one of the criteria below should be met • Tumour >4cm • Any tumour size with gross extra thyroidal extension • Distant metastases present	**All below criteria Should be met** • Tumour <1cm unifocal or multifocal • Classical papillary or follicular variant of papillary carcinoma, or follicular carcinoma • Minimally invasive without angioinvasion • No invasion of thyroid capsule (extra thyroidal extension)	**All other cases-** May benefit from RRA • Large tumour size • Extra-thyroidal extension • Unfavourable cell type (tall cell, columnar or diffuse sclerosing papillary cancer, poorly differentiated elements) • Widely invasive histology • Multiple lymph node involvement, large size of involved lymph nodes, high ratio of positive to negative nodes, extracapsular nodal involvement.

The benefits and side effects of RRA treatment is summarised in Table 1.14.

Table 1.14 Advantages and Disadvantages of RRA (Perros, Boelaert et al. 2014)

Advantages	Disadvantages/Side effects
- Eradication of all residual thyroid cells subsequent reduced risk of local and distant tumour recurrence (Hackshaw, Harmer et al. 2007) - Possible prolonged survival (Sawka, Thephamongkhol et al. 2004) -Destruction of all thyroid tissue providing reassurance to patients - Increased sensitivity of Tg monitoring facilitating early detection of recurrent or metastatic disease (Mazzaferri 1999) - Increased sensitivity of subsequent iodine scanning if required	- Nausea - Radiation cystitis, gastritis, bleeding - Need to avoid pregnancy (6 months) or fathering a child (4 months) - Increased risk of miscarriage in the first year - Painful thyroiditis - Sialadenitis - Xerostomia - Dysgeusia - Pulmonary fibrosis Second malignancies

RAI has shown to reduce the risk of local and distant metastases in high risk tumours (Sawka, Thephamongkhol et al. 2004). It's role in low risk tumours however remains less convincing (Hay, McConahey et al. 2002). It has shown to effective in dealing with recurrences and undetected metastases (Mazzaferri 1997). However, there is lack of firm evidence for the above and the treatment is not firmly established (Pacini, Schlumberger et al. 2005). A systematic review by Sawka et. al failed to confirm the use of radioiodine ablation in decreasing recurrences and cause specific mortality (Sawka, Brierley et al. 2008).

As is evident from Table 1.14, RAI is associated with significant side-effects ranging to neck pain and sialadenitis (Reiners, Dietlein et al. 2008) to serious and largely dose dependent complications including leukaemia and secondary solid tumours (Rubino, de Vathaire et al. 2003).

1.3.10 TSH suppression

In patient with thyroid cancer after thyroidectomy, thyroid hormone replacement therapy is required. This is not only to replace endogenous thyroid hormone but it is generally thought to inhibit tumour growth indirectly by its negative feedback effects on pituitary Thyroid Stimulating Hormone (TSH) secretion (Cooper, Specker et al. 1998). Thyroid hormone replacement is usually in the form of levothyroxine (T4). Usually a large T4 dose is required to suppress blood TSH levels below the normal range. This is called 'TSH suppression'.

Rationale and evidence for TSH suppression

DTC's express TSH receptor on the cell membrane and respond to TSH stimulation. This stimulation leads to increase in expression of several thyroid specific proteins namely thyroglobulin and sodium-iodine symporter, and increases rates of cell growth (Biondi and Cooper 2010). Hence suppression of TSH with high doses of T4 hormone is used in thyroid cancer patients in an attempt to decrease the risk of recurrences (McGriff, Csako et al. 2002; Piccardo, Arecco et al. 2013).

Evidence from many studies has shown that there are long term benefits from TSH suppression especially in high risk tumours. In one study, TSH suppression was an independent predictor of disease progression in patients with stage III or IV PTC, but not in those with low-risk tumours (Jonklaas, Sarlis et al. 2006; Hovens, Stokkel et al. 2007).

Another study by Pujol et al. showed that thyroid cancer patients with TSH levels that were consistently low had an improved rate of relapse-free survival compared with those whose with higher levels (Pujol, Daures et al. 1996). Decreased recurrences and mortality after TSH suppression is evident only in patients with high-risk differentiated thyroid cancers (Biondi and Cooper 2010).

BTA guidelines recommend evaluation of response and risk of recurrence according to Dynamic risk Stratification 9-12 months after initial treatment (Perros, Boelaert et al. 2014). In patients with an incomplete response serum TSH should be suppressed below 0.1 mU/l indefinitely. In patients who have an indeterminate response, it is

recommended to maintain serum TSH concentrations between 0.1 and 0.5 mU/l. In patients with an excellent response to treatment for thyroid cancer, the serum TSH should be maintained in the low-normal range between 0.3-2 mU/l.
The ATA recommends initial TSH suppression to below 0.1 mU/L for high and intermediate risk thyroid cancer patients, while maintenance of the TSH at or slightly below the lower limit of normal (0.1–0.5 mU/L) is considered appropriate for low-risk patients (Haugen, Alexander et al. 2016).

1.3.11 Thryoglobulin

Thyroglobulin (Tg) is commonly used in the follow-up of patients with PTC. It is a glycoprotein produced only by normal or neoplastic thyroid follicular cells (Ibrahimpasic, Nixon et al. 2012). Detection of Tg post total thyroidectomy and LN dissection indicates the presence of persistent thyroid tissue or disease (Francis and Schlumberger 2008). Therefore, it is of importance when less than total thyroidectomy has been performed. When proper total thyroidectomy and LN dissection is done, Tg level should be undetectable and hence any rise subsequently can be a good indicator of recurrent disease.

Chapter 2

Design and Aims of the Thesis

There are two types of surgical approaches employed in the treatment of cervical Lymph node metastasis in PTC namely 'prophylactic' and 'therapeutic' cervical lymph node dissection. The aim of the thesis was to investigate the role of cervical Lymph Node Metastasis and their long-term outcomes in the context of the above mentioned surgical approaches.

2.1 Primary Aims

1. To determine the incidence of cervical lymph node metastases in Papillary Thyroid Carcinoma.
2. To compare the long-term outcomes between prophylactic and therapeutic cervical lymph node dissection in PTC.

2.2 Secondary Aim

To establish if preoperative imaging reliably predicts nodal metastasis in the central and lateral compartment of the neck in papillary thyroid cancer.

The study is divided into two parts-

2.3 Part A

Systematic reviews

We conducted three systematic reviews as part of the thesis-

1. **Systematic review of Central Cervical LN metastases in PTC**
2. **Systematic review of Lateral Cervical LN metastases in PTC**
3. **Systematic review of Imaging of cervical LN metastases in PTC**

2.4 Part B

Multicentre Retrospective Cohort Study

This study covered a period of 9 years and data was collected from three major hospitals in London.

The individual systematic reviews and the Cohort study are discussed in separate chapters below.

Chapter 3

Systematic Review of Central Cervical Lymph Nodes Dissection in Papillary Thyroid Cancer

3.1 Aims and Objectives

1. To determine the extent of central cervical Lymph Node involvement in Papillary Thyroid cancer
2. To compare the outcomes between prophylactic and therapeutic central cervical LN dissection in PTC.

3.2 Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were applied:

Inclusion Criteria

- All studies of patients with papillary thyroid cancer undergoing either prophylactic or therapeutic lymphadenectomy of the central cervical lymph nodes published over 40 years from 1970-2009.
- Studies involving imaging modalities in the detection of central cervical LNs in PTC published over the last 10 years.

Exclusion Criteria

- All studies with less than 100 patients and/or less than 2 years follow up were excluded.

Keywords:

The following search terms were used always in combination with 'Papillary thyroid cancer' (PTC)- 'therapeutic central lymph node dissection', 'prophylactic central lymph node dissection' 'Recurrence', 'death', 'recurrence' and survival', 'radioiodine therapy' and 'radiotherapy'.

3.3 Methods

- An extensive search was conducted on the MEDLINE database via the Pubmed interface (http://www.ncbi.nlm.nih.gov/pubmed). ISI web of knowledge was used for forward and backward quotation search (http://apps.isiknowledge.com/).

- The search covered a 40-year period from 1970 up to October 2009 with the combination of above mentioned search terms. The search was restricted to the presence of these key words in the title or abstract of the articles.
- Preliminary search using these terms yielded 11,924 publications of which 1402 were identified according to the inclusion and exclusion criteria.
- Abstracts of all 1402 publications were further scrutinised for presence of relevant data. Out of these, 95 publications containing relevant data were read in full-text.
- This process identified 23 studies appropriate for analysis based on the criteria set out above. All 23 publications were subjected to forward and backward quotation searches using the Thompson resource 'ISI Web of Knowledge' (http://apps.isiknowledge.com/). This identified three further studies which are included. Hence a total of 26 studies were included in the analysis.
- Out of these 26 included studies, 21 provided data for central cervical lymph node dissection and 5 were imaging studies.
- 21 studies providing data for central cervical lymph node dissection are as follows- (Wada N 2003; Shindo, Wu et al. 2006; Sywak M 2006; Lee YS 2007; Roh JL 2007; Davidson HC 2008; Low TH 2008; Palestini N 2008; Se Jun Choi, Kyoung-Ja Cho et al. 2008; Son YI 2008; Bonnet S 2009; Chung YS 2009; Costa, Giugliano et al. 2009; Koo, Choi et al. 2009; Mercante G 2009; Moo TA 2009; Perrino M 2009; Rosenbaum MA 2009; Sadowski BM 2009; Wada N 2009; Zuniga S 2009).
- A standard proforma was used to extract data from the articles including details of the study population, type of surgical approach, imaging used to detect metastatic cervical LN, number of cervical lymph nodes positive on histology and any comparative results if available. All were retrospective cohort studies with no direct comparable data. There were no randomised controlled trials found in literature to enable a meta-analysis.

- There were no studies comparing outcomes between prophylactic and therapeutic cervical LN dissection.

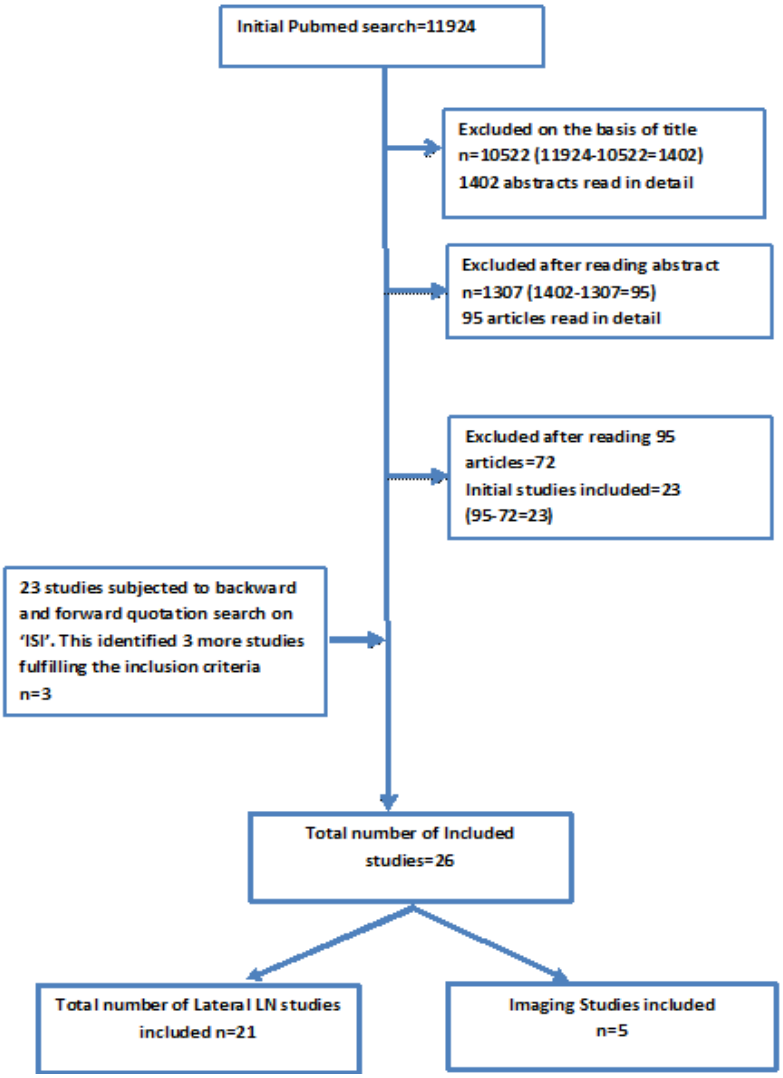
3.4 Statistical Methods

For analysis, standard procedures were not used as there was no study with combined comparative data for prophylactic and therapeutic LN dissection. To simplify the results, we have used simple percentages.

3.5 Results

Literature search yielded 21 studies which provided data were included in this review. Data was available for 4188 patients from 21 studies for prophylactic and therapeutic central LND. Fourteen studies provided results for only prophylactic central LND. Four studies provided results for therapeutic central LND and in three studies results were available for both prophylactic and therapeutic central LND. Figure 3.1 shows a flow chart detailing the process of inclusion and exclusion of studies for this review.

Figure 3.1 Flow chart illustrating the process of inclusion and exclusion of studies



The baseline characteristics and methodology of the included studies for central cervical LN are shown in Table 3.1

Table 3.1: Characteristics of included studies for central lymph nodes

Study	Year	Study Design	n	Imaging used in Pre-operatively	Type of Surgical Procedure	Comments
Shindo M	2006	Retrospective	100	None	Prophylactic	Study investigated incidence of positive LN in <45yrs vs >45yrs. Results showed 39% had positive LN in >45 yrs and 29% showed positive LN in 29%.
Swyak M	2006	Retrospective	447	USS	Prophylactic	Patients with tumours >1cm included. Patients were divided in two groups; Group A-TT+ Ipsilateral CLND, Group B-TT alone Study compared postablative stimulate Tg level and number of radioiodine treatments. The authors found Tg levels lower in Group A compared to the other group. No difference was found in the complication rates.
Lee YS	2007	Retrospective	103	USS	Prophylactic	Tumours <2 cms; USS negative for central LNM. Looked Serum Tg-concluded extent of CLND has no effect on Tg
Low TH	2008	Retrospective	100	USS	Prophylactic	This study looked at Tg levels at 12 months postop. They concluded that LN metastases is associated with increased postoperative Tg levels.

Son YI	2008	Retrospective	114	USS	Prophylactic	Patients divided into two groups; Group A-Comprehensive CLND (bilateral) and Group B (Unilateral). Complications and recurrence rates were compared at 2 years. Study found no difference in in recurrence rates between the two groups.
Costa S	2009	Retrospective Cohort	244	USS	Prophylactic LND	Study divided into two groups Group A- TT+ pCLND Group B- TT without CND
Koo BK	2009	Prospective	111	USS+CT	Prophylactic	Prospective non-randomised trial. Clinically and radiologically node negative patients included.
Zuniga S	2009	Historical Cohort	266	USS	Prophylactic LND	pCLND showed no advantage for neck recurrence
Moo TAS	2009	Prospective	104	USS	Prophylactic	Investigated if ipsilateral CLND was sufficient in tumours <1cm. They concluded that in tumours <1cm Ipsilateral CLND maybe Sufficient.
Choi JS 2008	2009	Retrospective	101	USS	Prophylactic	All patients had micro-carcinoma (<1cm). Patients divided into two groups- one with CLND and the other without CLND. There was no randomisation, the decision of CLND was based on surgeon's and patient's agreement. 37.5% with CLND had positive LN.
Bonnet S	2009	Retrospective	115	USS	Prophylactic	This study looked at RAI ablations treatment in patients with tumours <2cms. Central LN metastasis was found in nearly 37% of

						patients. These findings allowed selection of patients for RAI and modified the Indication for RAI in 30% of patients.
Perrino M	2009	Retrospective	251	USS	Prophylactic	This study evaluated the predictor of outcomes after CLND in Tumours <2 cms. They concluded that only lymph node metastases and extracapsular invasion were strongly associated with persistence and recurrence.
Mercante G	2009	Retrospective	445	USS	Prophylactic	All patients were micro-carcinoma (<1cm). Surgical treatment was variable according to time period it was performed. CLNM were present in 40% of patients. Recurrence was seen in 2.7%.
Chung YS	2009	Retrospective	245	USS+CT	Prophylactic CLN and Therapeutic LLND	This study included PTMC patients only. They looked at the incidence of skip metastases to lateral LN which was found to be 7.7%. The study recommended imaging to look for LN metastasis in all patients with PTMC.
Palestini N	2008	Retrospective Cohort study	305	NA	Mixture of Prophylactic and therapeutic	This study compared the complication rates between prophylactic and therapeutic CLND. No significant difference was found between the two groups.
Wada	2003	Retrospective	259	USS and Palpation	Mixture of Prophylactic and therapeutic	All included patients had PTMC. Patients were divided into two groups namely pCLND (Group A) and TT alone (Group B). They found no difference in terms of nodal recurrence between the two groups.
Wada	2009	Retrospective	120	USS+CT	Mixture of	All included patients were <20 years old. The study compared at

					Prophylactic and therapeutic	Disease Free Survival between patients undergoing prophylactic and therapeutic LND. They found DFS to be significantly better in pLND compared to tLND.
Rosenbaum	2009	Retrospective	110	USS, Palpation	Therapeutic	Patients were divided into two groups-TT +CLND (Group A) and TT alone (Group B). The study concluded that recurrences were uncommon after CLND but had higher rates of complications.
Roh JL	2007	Retrospective	155	Palpation	Therapeutic	The study Patients were divided in two groups- TT+CLND (Group A) and TT alone (Group B). They found that overall morbidity and hypocalcaemia was higher in the CLND group.
Sadowski BM	2009	Retrospective	310	USS, Palpation	Therapeutic	Patients were divided into two groups- CLND and no CLND-46.7% of patients with CLND had positive LN. All recurrences occurred in patients without CLND.
Davidson C	2008	Retrospective	183	USS, Palpation	Therapeutic	The study looked at incidence of LN metastases after different surgical procedures namely LN plucking, CLND and LLND. The highest rate of recurrence was found after LN plucking.

CLND-Central Lymph Node Dissection; LLND-Lateral Lymph Node Dissection; PTMC-Papillary Thyroid MicroCarcinoma

LND-Lymph Node Dissection; Tg-Thyroglobulin; RAI-Radio-iodine

NA-Not Available

Table 3.2 shows results of prophylactic and therapeutic central lymph node dissection in patients with papillary thyroid cancer (Mulla and Schulte 2012).

Table 3.2: Results of Central Lymph Node Dissection in Papillary Thyroid Carcinoma

Study	**Patients Total (n)**	**Methods to guide therapeutic central LND**	**Prophylactic central LND**		**Therapeutic central LND**	
			n	**p LN +**	**N**	**p LN +**
Costa S 2009	244		126	59	na	na
Zuniga S 2009	266		136	112	na	na
Koo BK 2009	111		111	60	na	na
Lee YS 2007	103		103	39	na	na
Shindo M 2006	100		94	33	na	na
Moo TAS 2009	104		104	47	na	na
***Choi JS 2008**	101		48	18	na	na
Son YI 2008	114		114	52	na	na
Bonnet S 2009	115		115	42	na	na
Perrino M 2009	251		92	39	na	na
Mercante G 2009	445		226	112	na	na
Low TH 2008	100		40	26	na	na
Swyak M 2006	447		56	21	na	na
Chung YS 2009	245		206	45	na	na
Palestini N 2008	305	Na	93	20	64	46
Wada 2009	120	US, CT	47	30	73	72
***Wada 2003**	259	Palpation	235	143	24	23
Σ1	**3430**		**1946**	**898**		

Rosenbaum 2009	110	US, palpation	na	na	22	17
Roh JL 2007	155	Palpation	na	na	56	51
Sadowski BM '09	310	US, Palpation	na	na	180	125
Davidson C 2008	183	US, Palpation	na	na	19	12
Total (Σ2)	**1442**				**438**	**346**
Total (Σ)	**4188**					
Percentages			**898/1946= 46.1 %**		**346/438= 79%**	

US-ultrasonography; CT-computerised tomography; pLN-histologically proven positive LN;

Σ1-total number of patients included in the prophylactic LN dissection group;

Σ2- total number of patients included in the therapeutic LN dissection group;

Σ- grand total number of patients in both groups; na=Not available/applicable

Total: 1244 (898 + 346)/4188 = 29.7%; prophylactic only: 898/3430 = 26.2%; therapeutic only: 346/1442 = 24%;

*Papillary Microcarcinoma <1cm.

A total of 4188 patients underwent therapeutic and/or prophylactic central LND, out of which 1244 had positive LN on histology (29.7%). Prophylactic central LND alone was performed in 1946 patients, of which 898 had positive central LN at surgery (46.1 %). A total of 1442 patients were assessed by various pre-operative methods for the presence of central LN. Therapeutic central LN dissection was performed in 438/1442 (30.4 %) patients guided by clinical examination and/or imaging.
Of the 438 patients who underwent therapeutic central LND, positive central LN were found in 79% (346/438). Hence 24% (346/1442) of patients who were evaluated for therapeutic central LND were found to have positive central LN at surgery.

There were six studies in the review that provided results of primary tumours less than 2 cms. These include two studies with papillary microcarcinoma (Wada 2003 and Choi 2008). Table 3.3 shows the results of CLND of these six studies. Out of 819 patients with small primary tumours, LN metastases were found to be positive in 48% of patients (393/819).

Table 3.3 Results of Central Lymph Node Dissection (CLND) for papillary carcinoma <2 cm

Study	Patients Total (n)	Prophylactic central LND		Therapeutic central LND	
		n	p LN +	N	p LN +
Mercante(2009)	445	226	112	na	na
Bonnet (2009)	115	115	42	na	na
Perrino (2009)	251	92	39	na	na
Choi (2008)	101	48	18	na	na
Lee(2007)	103	103	39	na	na
Wada(2003	259	235	143	24	23
Total	**1274**	819	393	na	na
Percentages	**393/1274=30.8%**	**393/819=48%**			

na-Not available/applicable

In Table 3.4 are shown results of CLND according to primary tumour size. The results provided from three studies with patients classified as having tumours less than or greater than 1 cm. In tumours <1 cm, out of a total of 143 patients, 37 were found to have positive central lymph nodes (CLN) (26%). Out of 143 patients with tumours >1 cm, 106 were found to be positive for metastases (74%).

Table 3.4 Results of central lymph node dissection according to the size of primary tumour

Study	Patients Total (n)	Total pN+	<1cm	>1cm
Moo (2009)	104	45	**16**	**29**
Koo (2009)	111	56	7	49
Bonnett(2009)	115	42	14	28
Total	330	143	37	106
Percentages			**37/143=25.9%**	**106/143=74.1%**

Two included studies provided results according to the T stages as shown in Table 3.5. In patients classified as T1–T2, a total of 50 patients showed metastases out of 88 (57%). In T3–T4 patients, 38 were positive out of a total of 88 (43%).

Table 3.5 Results of central lymph node dissection according to T stage

Study	Patients Total (n)	Total pN+	T1-2	>T3
Shindo (2006)	100	**33**	**23**	**10**
Costa (2009)	126	55	27	28
Total	226	88	50	38
Percentages			**50/88=56.8%**	**38/88=43.2%**

The results of imaging for both central and lateral cervical lymph nodes are discussed collectively in chapter 5.

3.6 Discussion-Central Cervical Lymph Node Dissection

3.6.1 Advantages of prophylactic Central LND

There are several arguments in favour of pCLND. The high incidence of metastatic central cervical LN is one of the strong arguments. From our systematic review of central LND, the frequency of metastatic LN was 46.1% in prophylactic and 79% in the therapeutic approaches (Table 3.2). In tumours <2cms, which is T1 stage according to AJCC Cancer Staging (Cooper, Doherty et al. 2009), 48% patients showed metastases in CLN. According to ATA, 90% of patients with PTC will have microscopic metastatic disease in the cervical LN. (Cooper, Doherty et al. 2006). It is quite clear from these figures that central cervical metastases are found in a large proportion of patients with PTC. It is worth pointing out that even in T1 patients nearly half would be found to have metastatic LN if central LN are dissected prophylactically. Performing pCLND would therefore be crucial in complete staging and guide adjuvant radio-iodine treatment (Bonnet, Hartl et al. 2009).

Another important argument is high loco-regional recurrence found in PTC. Loco-regional recurrence rates in PTC are nearly 30% (Hay, Bergstralh et al. 1999; Leboulleux, Rubino et al. 2005). Several studies have shown that patients with initial nodal involvement have a higher rate of recurrence (Scheumann, Gimm et al. 1994; Hughes, Shaha et al. 1996; Davidson, Park et al. 2008; Soyluk, Selcukbiricik et al. 2008). Leaving behind occult metastatic LN hence would predispose these patients to recurrences. An older study of 1,355 patients with 30 years of follow-up showed the likelihood of cancer death was increased by regional lymph-node metastases in patients without distant metastases (Mazzaferri and Jhiang 1994).

Studies have shown that performing neck dissection on patients with lymph node metastases decreases the rate of regional recurrences and improves survival (Pereira, Jimeno et al. 2005; White, Gauger et al. 2007).

Re-operative surgery to remove central LN is more challenging and puts the recurrent laryngeal nerve and parathyroid glands at increased risk (Shindo, Wu et al. 2006; White and Doherty 2007). This higher incidence of recurrent laryngeal nerve

and hypo-parathyroidism after re-operative surgery is another reason to perform pCLND. (Pattou, Combemale et al. 1998; Kim, Mandel et al. 2004).

3.6.2 Disadvantages of prophylactic Central LND

Complications that can arise from central LN dissection are important factors which prevents against widespread adoption of prophylactic CLND (pCLND). Transient hypo-parathyroidism is a common complication associated with CLND (Chan, Lang et al. 2013), incidence of this has been reported anywhere between 14-44% (Mazzaferri EL 2009). Other complications include transient and permanent recurrent laryngeal nerve palsy. The incidence is 4-7.3% to 0-3.6% respectively.

Many studies have shown no difference in the complication rates between pCLND and therapeutic CLND when performed by experienced surgeons (Roh, Park et al. 2007; Xiao and Gao 2010). A recent systematic review showed a significant increase of transient hypocalcaemia in pCLND patients compared to those who underwent total thyroidectomy alone (Zhu, Zhong et al. 2013). However, the same review also found no significant difference in the incidence of permanent hypocalcaemia, temporary and permanent vocal cord palsy (Zhu, Zhong et al. 2013).

Another argument against pCLND is that the presence of positive lymph nodes does not affect prognosis and survival in papillary thyroid carcinoma (Shaha, Shah et al. 1996; Sato, Oyamatsu et al. 1998). Some conclude that there is limited benefit for either disease recurrence or survival outcomes (Grebe and Hay 1996) and hence should be performed only in patients deemed high risk: larger tumours, extra-thyroidal extension or aggressive histological subtypes (Iyer and Shaha 2011). Despite the above arguments, evidence from a large database of more than five thousand patients indicated that LN metastases has a negative impact on survival and a significantly higher mortality (Odds ratio=2.5; 95% CI, 1.6-4.1) (Lundgren, Hall et al. 2006). A literature review by White and colleagues concluded that addition of pCLND will add survival benefit to PTC patients (White, Gauger et al. 2007). pCLND has shown to reduce morbidity associated with potential reoperation, reduces the risk of central neck lymph node recurrence, provides more accurate information for staging, and facilitates postoperative radioactive iodine administration as well as

long term follow-up (Moo and Fahey ; Hughes, Shaha et al. 1996; Sawka, Brierley et al. 2008). A recent systematic review on the oncologic outcomes after pCLND showed that recurrence free survival may improve after pCLND although this was supported by low level evidence (Mamelle, Borget et al. 2015).

A recent consensus report by the European Society of Endocrine Surgeons (ESES) analysed thirty studies and five meta-analyses on pCLND (Sancho, Lennard et al. 2014). It acknowledged the lack of randomized clinical trials on the subject, and the heterogeneity of study populations was the main limiting factors to draw clear conclusions. However, based on the available literature, they suggest that pCLND should be risk-stratified. Larger tumours (T3,T4), patients aged 45 years and older or 15 years and younger, males, bilateral or multifocal tumours and patients with known involved lateral lymph nodes were all clear candidates for pCLND (Sancho, Lennard et al. 2014). On the other hand, very low risk patients, <45-year-old females with unilateral unifocal T1a tumours will probably not benefit from pCLND (Sancho, Lennard et al. 2014). They also recommend the procedure should be limited to surgeons who have the available expertise and experience.

As is clear from the above discussion, pCLND is still an unresolved issue but it is becoming a more common practice amongst surgeons (Moo and Fahey 2011).

3.7 Limitations

1. The review was not registered in accordance with PRISMA guidelines on databases such as PROSPERO. However, in hindsight it would have been better to have registered these on similar databases to ensure the consistency and quality of reporting.

2. The quality of the included studies has not been assessed.

3. There were no studies found comparing outcomes between prophylactic and therapeutic central cervical LN dissection. Hence outcomes comparing the two methods were not evaluated.

Chapter 4 Systematic Review of Lateral Cervical Lymph Nodes Dissection in Papillary Thyroid Cancer

4.1 Aims and Objectives

1. To determine the extent of lateral cervical Lymph Node involvement in Papillary Thyroid Carcinoma
2. To compare the outcomes between prophylactic and therapeutic lateral cervical LN dissection in PTC.

4.2 The following inclusion and exclusion criteria were applied to the review:

Inclusion Criteria

- All studies of patients with papillary thyroid cancer undergoing either prophylactic or therapeutic lymphadenectomy of the lateral cervical lymph nodes published over 41 years (1970-2011).
- Studies involving imaging modalities in the detection of lateral cervical LNs in PTC published over the 12 year (1999-2011).

Exclusion Criteria

- All studies with less than 100 patients and/or less than 2 years follow up were excluded.

Keywords:

The following search terms were used always in combination with 'Papillary thyroid cancer', 'lateral lymph node dissection', 'therapeutic lateral lymph node dissection', 'prophylactic lateral lymph node dissection', 'recurrence', 'survival', 'Recurrence', 'death', 'radioiodine therapy' and 'radiotherapy'.

4.3 Methods

- An extensive search was conducted on the MEDLINE database via the Pubmed interface (http://www.ncbi.nlm.nih.gov/pubmed). ISI web of knowledge was used for forward and backward quotation search (http://apps.isiknowledge.com/).
- The search covered over a 41-year period (1970-2011). A combination of above mentioned search terms was used. The search was restricted to the presence of these key words in the title or abstract of the articles.

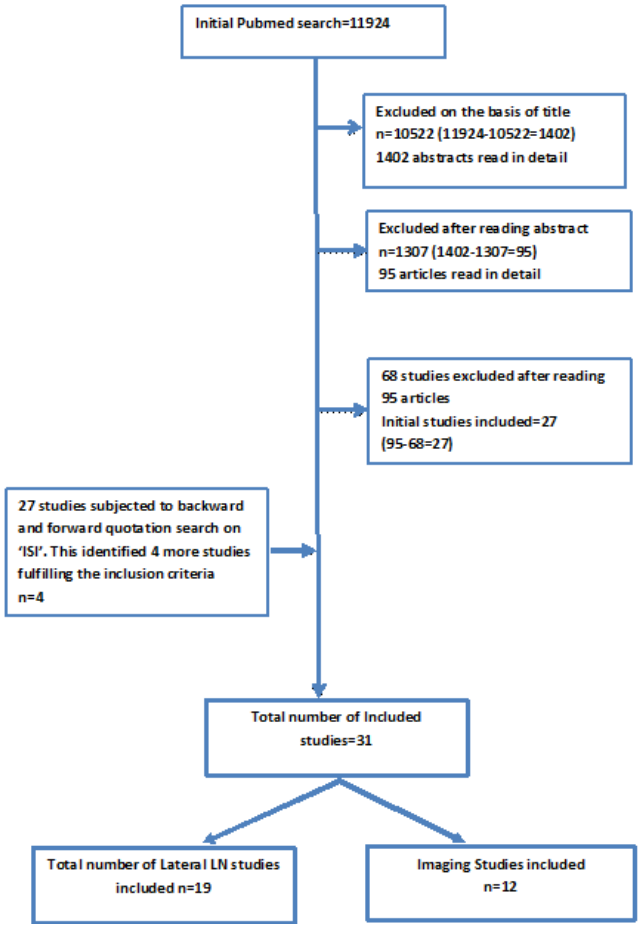
- Preliminary search using these terms yielded 11,924 publications of which 1402 were identified according to the inclusion and exclusion criteria.
- Abstracts of all 1402 publications were further scrutinised for presence of relevant data. Out of these, 95 publications containing relevant data were read in full-text.
- This process identified 27 studies appropriate for analysis based on the criteria set out above. All 27 publications were subjected to forward and backward quotation searches using the Thompson resource 'ISI Web of Knowledge' (http://apps.isiknowledge.com/). This identified four further studies, which are included in the analysis. Hence a total of 31 studies were included in the analysis.
- Out of these 31 included studies, 19 provided data for lateral cervical lymph node dissection and 12 were imaging studies.
- 19 studies included in the analysis are as follows-(Patron, Bedfert et al. ; Attie 1988; Wada, Duh et al. 2003; Ito, Higashiyama et al. 2007; Roh, Park et al. 2007; Davidson, Park et al. 2008; Kim, Park et al. 2008; Low, Delbridge et al. 2008; Palestini, Borasi et al. 2008; Sugitani, Fujimoto et al. 2008; Wada, Masudo et al. 2008; Bonnet, Hartl et al. 2009; Choi, Kim et al. 2009; Chung, Kim et al. 2009; Kwak, Kim et al. 2009; Perrino, Vannucchi et al. 2009; Roh, Park et al. 2009; Sadowski, Snyder et al. 2009; Wada, Sugino et al. 2009)**.**
- A standard proforma was used to extract data from the articles including details of the study population, type of surgical approach, imaging used to detect metastatic cervical LN, number of cervical lymph nodes positive on histology and any comparative results if available.
- There were no randomised controlled trials found in literature to enable a meta-analysis. All were retrospective cohort studies with no direct comparable data.
- There were no studies comparing outcomes between prophylactic and therapeutic cervical LN dissection.

4.4 Statistical Methods For analysis, the standard procedures were not used as there was no study with combined comparative data for prophylactic and therapeutic LN dissection. To simplify the results, we have used simple percentages.

4.5 Results

Nineteen studies provided data for lateral cervical LND and were included in this systematic review. Data was available for 5587 patients from 19 studies for prophylactic and therapeutic lateral LND. All were cohort studies and no randomised controlled trials were found in the literature. Three studies provided results for prophylactic lateral LND alone. In fifteen studies the results were mixed for therapeutic and prophylactic lateral LND or therapeutic lateral LND alone. One study provided results for prophylactic lateral LND in 50% of the patient cohort; the remaining half underwent therapeutic LN dissection for which the results were unavailable (Attie 1988). Figure 4.1 shows flow chart illustrating the process of inclusion and exclusion of studies in the systematic review for lateral LN**.**

Figure 4.1 Flow chart detailing the process of inclusion and exclusion of studies



The baseline characteristics and methodology of the included studies for lateral cervical LN are shown in Table 4.1

Table 4.1 Characteristics of included studies for lateral lymph nodes

Study	Year	Study Design	n	Imaging used in Pre-operatively	Type of Surgical Procedure	Study Details
Attie, J. N	1998	Retrospective	313	Palpation	Prophylactic and Therapeutic	Historical study-patient cohort included other types of thyroid cancers in addition to PTC(287/313). Nine patients with PTC died of the disease.
Bonnett S	2009	Retrospective	115	USS	Prophylactic	Cohort included T1 tumours only (<2 cms). All patients underwent CLND in addition to pLLND. Only one patient had laryngeal palsy. pLND modification the indication for RAI in 30% of patients.
Ito Y	2007	Retrospective	1231	USS	Prophylactic	The study investigated the incidence of lateral LN metastasis. All included patients were N0. The authors concluded that incidence of LLNM increased significantly with tumour size as did Lymph Node DFS.
Patron V	2011	Retrospective	131	USS, Palpation	Prophylactic	This study looked at the pattern of lateral LNM in N0 patients. Only tumours >1cm were included. They concluded occult LNM was most common in neck levels III, IIa, IV and Vb.

Wada	2003	Retrospective	259	USS, Palpation	Mixture of Prophylactic and therapeutic	All included patients had PTMC. Patients were divided into two groups namely MRND (Group A) and TT alone (Group B). They found no difference in terms of nodal recurrence between the two groups; pLLND was not recommended.
Wada	2008	Retrospective	231	USS, Palpation	Prophylactic and therapeutic	This study included patients with tumours >1cm. Clinical outcomes according to age and nodal status were evaluated. The study concluded that prognosis was worse in patients aged >45 and palpable LN.
Wada	2009	Retrospective	120	USS, CT	Mixture of Prophylactic and therapeutic	All included patients were <20 years old. The study compared at Disease Free Survival between patients undergoing prophylactic and therapeutic LND. They found DFS to be significantly better in pLND compared to tLND.
Roh JL	2007	Retrospective	155	Palpation	Therapeutic	The study Patients were divided in two groups- TT+CLND+LLND (Group A) and TT alone (Group B). They found that overall morbidity and hypocalcaemia was higher in the CLND group. Prophylactic LND was not recommended based on recurrences, pattern etc.
Perrino M	2009	Retrospective	251	USS	Therapeutic	This study evaluated the predictor of outcomes after CLND

						in Tumours <2 cms. All patients underwent pCLND and tLLND. They concluded that lymph node metastases and extracapsular invasion were strongly associated with persistence and recurrence.
Sadowski BM	2009	Retrospective	310	USS, Palpation	Therapeutic	Patients in this study had routine CLND and tLLND. They complications rates especially recurrent laryngeal nerve injury was low and the study concluded that CLND can be performed safely in experienced hands.
Palestini N	2008	Retrospective Cohort Study	305	NA	Prophylactic and Therapeutic	This study compared the complication rates between prophylactic and therapeutic CLND. In addition, patients also had tLLND if lateral LN were 'evident'. No significant difference was found in terms of permanent morbidity between the two groups.
Davidson C	2008	Retrospective	183	USS, Palpation	Therapeutic	The study looked at incidence of LN metastases after different surgical procedures namely LN plucking, CLND and LLND. The highest rate of recurrence was found after LN plucking
Chung YS	2009	Retrospective	245	USS+CT	Prophylactic CLN and Therapeutic	This study included PTMC patients only. They looked at the incidence of skip metastases to lateral LN which was found to be 7.7%. The study recommended imaging to

					LLND	look for LN metastasis in all patients with PTMC.
Low TH	2008	Retrospective	100	USS	Therapeutic	This study looked at Tg levels at 12 months follow-up. Patients underwent pCLND and tLLND. They concluded that LN metastases is associated with increased postoperative Tg levels.
Kwak JY	2009	Retrospective	671	USS	Therapeutic	Study included only PTMC patients. Only patients with USS confirmed LN underwent LND. The study evaluated USS features in PTMC that could predict lateral LNM.
Sugitani I	2008	Prospective	361	USS	Therapeutic	PTMC patients were excluded from the study. This study evaluated the accuracy of USS in predicting LNM. They concluded CLND was sufficient if no lateral LN were found on USS.
Choi JS	2009	Retrospective	299	USS, CT	Therapeutic	Study compared diagnostic accuracy of USS versus CT in evaluating metastatic cervical LN. All patients underwent pCLND and tLLND as indicated. They concluded that high resolution USS was better than CT for lateral LNM and vice versa for central LNM.
Roh JL	2009	Prospective	133	USS, CT	Prophylactic and therapeutic	Study evaluated use of USS in detecting cervical LNM. All patients had pre-operative USS and underwent CLND. Pre-operative USS findings were compared to final histology

						results.
Kim E	2008	Retrospective	165	USS, CT	Therapeutic	This study compared diagnostic accuracy of USS versus CT in evaluating metastatic cervical LN. Pre-operative USS and CT findings were compared to final histology results. The study concluded that combination of USS and CT was superior to USS alone in the detection of metastatic lateral cervical LN.

CLND-Central Lymph Node Dissection

LLND-Lateral Lymph Node Dissection

LLNM-Lateral Lymph Node Metastasis

PTMC-Papillary Thyroid MicroCarcinoma

LND-Lymph Node Dissection

pLND- prophylactic Lymph Node Dissection

Tg-Thyroglobulin

RAI-Radio-iodine

NA-Not Available

DFS-Disease Free Survival

Table 4.2 shows results of prophylactic and therapeutic lateral lymph node dissection in patients with papillary thyroid cancer.

Table 4.2: Results of Lateral Lymph Node Dissection in Papillary Thyroid Carcinoma (Mulla, Knoefel et al. 2012)

Study	**Patients Total (n)**	**Methods to guide therapeutic lateral LND**	**Prophylactic lateral LND**		**Therapeutic lateral LND**	
			n	p LN +	n	p LN +
Bonnet S 2009[a]	115		115	12	na	na
Ito Y 2007	1231		1231	790	na	na
Patron V 2011	140		131	26	na	na
Attie JN 1998[°]	313	Palpation	155	94	158	na
Wada 2003[*]	259	Palpation	185	86	24	24
Wada 2008	231	Palpation	201	151	30	na
Wada 2009**	120	US, CT	30	18	na	na
Total (Σ1)	2409		2048	1177		
Roh JL 2007	155	Palpation	Na	na	26	23
Perrino M 2009	251	US, Palpation	Na	na	35	26
Sadowski BM 2009	310	US, Palpation	Na	na	33	30
Palestini N 2008	305	Na	Na	na	33	33
Davidson C 2008	183	US, Palpation	Na	na	73	61
Low TH 2008	100	US, Palpation	Na	na	8	7
Chung YS 2009	245	US, CT	Na	na	39	3
Kwak JY 2009	671	US	Na	na	26	25
Sugitani I 2008	361	US	Na	na	130	127
Choi JS 2009	299	US, CT	Na	na	53	29
Roh JL 2009	133	US, CT	Na	na	34	34
Kim E 2008	165	US, CT	Na	na	52	24
Total (Σ2)	3178				566	446
Total (Σ)	5587					
Percentage of positive Lymph node			1177/2048=57.5%		446/566= 78.8%	

US-ultrasonography; CT-computerised tomography; pLN-patients with histologically proven positive LN; Σ1- total number of patients included in the prophylactic LN dissection group only; Σ2- total number of patients included in the therapeutic LN dissection group only; Σ, grand total number of patients in both groups; na- not available.

*Only T1 tumours were included; of these, 44% were micro-carcinomas, i.e., <1 cm.

†Results of patients undergoing only prophylactic surgery (n = 155) available.

‡PTMC: papillary thyroid micro carcinoma. The remaining 50 patients underwent prophylactic central LN dissection

§Data from children.

Total of 5587 patients underwent therapeutic and/or prophylactic lateral LND, out of which 1,623 had positive LNs on histology (29.1%). Prophylactic lateral LND alone was performed in 1447 patients, of which 828 had positive lateral LN at surgery (57.2%). In total, 2048 patients underwent prophylactic lateral LND out of which 1177 were found to have metastatic positive lateral LN on histology (57.5%).
In the therapeutic category, a total of 4101 patients were assessed by various pre-operative methods for the presence of lateral LN. From the available data, therapeutic lateral LN dissection was performed in 566/3437 (16.5%) patients guided by clinical examination and/or imaging. Of these 566 patients, positive lateral LN were found in 446 (78.8%). Table 4.3 shows results of prophylactic lateral LN metastases depending on stage of the tumour. The percentage of lateral LN metastases in T1, T2 and T3/T4 tumours was 49·2%, 72·5% and 86·5%, respectively.

Table 4.3 T stage-dependent frequency of lateral lymph node (LN) metastases detected by prophylactic LN dissection (Ito 2007) Total n = 1231

Size of primary (cms)	Patients with positive lateral LNs/total number of patients	T stage (UICC VI)	Patients with positive lateral LNs/total number of patients
<1	53/131 (40·5%)	T1	261/530 (49·2%)
1.1-2.0	208/399 (52·1%)	T2	401/553 (72·5%)
2.1-3.0	257/368 (69·8%)	T2	
3.1-4.0	144/185 (77·8%)	T2	
>4.1	128/148 (86·5%)	T3+T4	128/148 (86·5%)
Total	790/1231 (64·2)	T1-T4	790/1231 (64·2%)

4.6 Discussion-Lateral cervical LN dissection

The treatment of lateral LN metastases is the most contentious area in the management of PTC. For decades, there has been considerable controversy regarding the type of surgical approach and the extent of lateral cervical lymph node dissection in PTC. One of the main reasons for this controversy is the lack of conclusive data which will provide us with useful information to formulate treatment plans.

The site of metastases to cervical LN varies according to studies. Some authors report ipsi-lateral central neck to be the most common site of metastases. (Qubain, Nakano et al. 2002; Roh, Park et al. 2007). The risk is reported to be greatest for lateral LN of levels II, III, and IV (Wada, Duh et al. 2003). Tumours arising from the upper pole often spread to the ipsi-lateral lateral compartment whereas those arising from the mid and lower pole favour the central compartment (Park, Lee et al. 2012; Zhang, Wei et al. 2012). This pattern of metastatic LN involvement can be attributed to the lymph drainage of the thyroid gland, which follows its venous

system. The frequency of skip metastases has been reported between 11.1%- 37.5% (Lee, Shin et al. 2014).

The frequency of metastatic LN found in the lateral compartment varies. In our systematic review, the frequency of metastatic LN in the lateral compartment was found to be 57.5% where prophylactic LND was performed. One study (Ito, Higashiyama et al. 2007) provided the results according to T stage; they found the incidence of metastatic lateral LN to be 40% even in T1 tumours. From our own data, metastatic lateral LN were found to be positive in 70% of patients who had prophylactic LND which confirms the finding from published work.

This high percentage of lateral metastatic LN found on prophylactic LND exposes significant pitfalls in the staging and subsequent management of these patients. Leaving behind these metastatic LN will lead to gross under-staging in these patients. Survival in different stages of PTC varies considerably according to the AJCC cancer staging (Edge SB 2010). Stage I and II have excellent prognosis but the survival drops to as low as 50% in stage IV. The staging progresses from I to III in the presence of LN metastases except in women <45 years of age who remain stage I. Under-staging of these patients will have a negative impact on their long-term outcomes and survival (Mulla and Schulte 2012).

Studies have shown that patients with clinically proven metastases to the lateral compartment are more likely to have recurrences and have shorter disease free survival (Ito Y 2010; de Meer, Dauwan et al. 2012). Clinically proven cervical LN metastasis at the time of initial surgery has been shown to be an independent risk factor of tumour recurrence (Ito Y 2010; Bozec, Dassonville et al. 2011). A recent study of over 800 cases of PTC found that N1 patients treated with only TT and RAI had about 60% a risk of persistent disease (Guy, Hirsch et al. 2014). From our own cohort, there were no recurrences in patients who had prophylactic LND; whereas there were 9 recurrences in those with therapeutic LND.

Loco-regional recurrent disease in PTC can vary anywhere between 8-23% (Kwang-Min Kim 2012) and about 75% of these local recurrences occur in the cervical lymph

nodes (Hong SJ 2001). Although the majority of the recurrences happen in the first ten years after surgery, about 20% of these can happen between 10-20 years (Grogan, Kaplan et al. 2013). It has been reported that 10% of patients with local recurrences and 50% with distant recurrence will die of the disease (Mazzaferri and Jhiang 1994). Recurrences in the lateral cervical compartment are twice as common as the central compartment (Kruijff, Petersen et al. 2013). Patients with clinically proven metastases to the lateral compartment are more likely to develop recurrences and have shorter disease free survival (Ito Y 2010; de Meer, Dauwan et al. 2012). Also presence of central metastases has shown to be an independent prognostic factor for lateral node recurrence disease (Barczynski, Konturek et al. 2013). Advanced age, male sex, cervical metastasis and tumour size are the most important factors for higher recurrence (Ito, Higashiyama et al. 2007; Kim, Park et al. 2012).

4.6.1 Disadvantages of prophylactic Lateral LND

Complications that can arise from lateral cervical LND is one of the main arguments against adopting prophylactic LND. Minor chyle leak occurs in the region of 2.3%. Thoracic duct injury needing re-operation for repair is low, reported to be around 0.6%. (Ito, Higashiyama et al. 2007; Ducoudray, Tresallet et al. 2013). The incidence of phrenic nerve injury, facial nerve paralysis, accessory nerve paralysis and Horner syndrome is also low in the range between 0.2% and 0.3% (Simon, Goretzki et al. 1996; Ito, Miyauchi et al. 2007).

Another source of controversy against the rationale for prophylactic LND is the uncertainty of the long-term outcomes from microscopic lateral LN metastases. (Lundgren, Hall et al. 2006; Bardet, Malville et al. 2008). There are no clinical predictive factors for LN recurrences and the role of imaging in detecting these metastasis is limited. The above argument is flawed on two levels. Firstly, the lack of high level of evidence notably from randomised controlled trials makes it impossible to draw definitive conclusions on survival and outcomes. The available data is from cohort studies which are mostly retrospective hence rendering results open to debate. Secondly PTC being a slow growing tumour, recurrence and not survival is considered to the outcome of interest in PTC (Sakorafas, Sampanis et al. 2010).

4.6.2 Advantages of prophylactic Lateral LND

There are several advantages of prophylactic LLND. It reduces the risk of recurrences in the cervical LN hence reducing the morbidity associated with re-operations (Ito, Kudo et al. 2012). About 10% of patients with local recurrence and 50% of those with distant metastasis will die of the disease (Mazzaferri and Jhiang 1994). Reoperations may be associated with high complication rates, such as injury to the recurrent laryngeal and spinal accessory nerve, hypoparathyroidism, and unsightly surgical scars (Esnaola, Cantor et al. 2001). For these mentioned reasons recurrence and not survival is considered to the outcome of interest in PTC (Sakorafas, Sampanis et al. 2010).

pCLND provides more accurate information for staging more than half of patients with positive central LN who will have metastatic lateral LN. Imaging methods namely Ultrasonography and Computerised Tomography do not have the required sensitivity and specificity to detect metastatic cervical LN (Hartl, Leboulleux et al. 2012). Hence performing pLLND remains the most reliable method of accurately staging patients with PTC (Hartl, Leboulleux et al. 2012).

Re-operations in the cervical compartments are usually performed for recurrences and persistent disease. This is technically challenging and is associated with increased incidence of recurrent laryngeal nerve injury, persistent hypo-parathyroidism, spinal accessory nerve injury, thoracic duct injury and unsightly scars. (Shindo, Wu et al. 2006; White and Doherty 2007; Sakorafas, Sampanis et al. 2010).

There are several studies which recommend prophylactic (Simon, Goretzki et al. 1996; Lundgren, Hall et al. 2006) lateral LND and have shown improved disease free survival (DFS) particularly in older male patients with larger tumours (Ito, Higashiyama et al. 2007). Studies have shown that prophylactic LND reduces the chances of recurrences and re-operations in both central and lateral compartment (Ito Y 2010; Popadich, Levin et al. 2011).

A recent in-depth review on surgical management of metastatic lateral LN recommends prophylactic lateral LND in tumours arising from upper pole, extensive ipsi-lateral or bilateral involvement of central compartment (Dralle and Machens

2013). This was based on the observation that tumours of the upper thyroid pole skip the central compartment spreading directly to the superior lateral nodes (Park, Lee et al. 2012; Zhang, Wei et al. 2012).

The complications and morbidity rates quoted against pLLND are low in experienced hands and can be tolerated in view of the benefit achieved by the operation (Harness, Fung et al. 1986; Attie 1988; Ducoudray, Tresallet et al. 2013).

The case to limit cervical LND to therapeutic as opposed to prophylactic is not evidence based. The evidence in support of prophylactic LN dissection is provided by many studies especially in high risk groups namely men, multi-focal tumour and extra-thyroidal tumour extension (So YK 2010), in which they have been shown to improve disease free survival (Ito, Higashiyama et al. 2007). Most clinicians agree that prophylactic LND allows for accurate staging of the disease that may guide subsequent treatment and follow-up (Pacini, Schlumberger et al. 2006)**.**

4.7 Limitations of the review

1. The review was not registered in accordance with PRISMA guidelines on databases such as PROSPERO. In hindsight we would have preferred to have this registered on similar databases to ensure the consistency and quality of reporting.
2. The quality of the included studies has not been assessed.
3. There were no studies found comparing outcomes between prophylactic and therapeutic lateral cervical LN dissection. Hence outcomes comparing the two methods were not evaluated.

Chapter 5

Systematic Review of Imaging of Metastatic Cervical Lymph Nodes metastases in Papillary Thyroid Cancer

5.1 Aims and Objectives

Primary Objectives

1. To understand if the commonly reported 'sensitivity' of imaging techniques is based on factual evidence.

Secondary Objective

1. To determine the diagnostic accuracy of USS and CT in detecting metastatic cervical LN.

2. To determine the usefulness of other imaging modalities namely MRI, 18-FDG PET/CT in detecting metastatic cervical LN.

5.2 Inclusion/Exclusion Criteria

The following inclusion criteria were used for this systematic review.

- Studies involving imaging modalities in detection of cervical lymph nodes in Papillary Thyroid Cancer published over a 17-year period (1995-2011)
- All studies had to be published in English.

Keywords

The following search terms were used always with combination with 'papillary thyroid cancer' (PTC)- 'LN dissection', 'sensitivity', 'specificity', 'therapeutic LN dissection, 'Ultrasound'(USS), 'Computerised Tomography' (CT), Magnetic Resonance Imaging' (MRI) and '18FDG PET–CT'. The search was restricted to the presence of one or more of these key words in the title or abstract of the articles.

5.3 Methods

- An extensive search was conducted on the MEDLINE database via the Pubmed interface (http://www.ncbi.nlm.nih.gov/pubmed). ISI web of knowledge was used for forward and backward quotation search (http://apps.isiknowledge.com/).

- The search covered a period of 17 years. A combination of above mentioned search terms was used. The search was restricted to the presence of these key words in the title or abstract of the articles.
- Preliminary search using these terms yielded 1129. Abstracts of all 1129 publications were scrutinised for presence of relevant data. Out of these, 32 publications containing relevant data were identified.
- These 32 publications were read in full text and scrutinised for the presence of relevant data. This process identified 28 studies appropriate for analysis based on the criteria set out above.
- Sixteen studies looked at sensitivity of USS, eight studies provided data for CT scan, one study involved MRI (31) and three studies provided data for 18FDG PET–CT
- A standard proforma was used to extract data from the articles including details of the study population, number of LN detected by imaging, site of metastatic LN detected, percentage of positive LN on histology, sensitivity, specificity, positive predictive value and negative predictive value.
- There were no randomised controlled trials found in literature to enable a meta-analysis.
- The included studies are as follows-
- 16 studies looked at sensitivity of US (Lee, Kawata et al. ; Yoon, Kim et al. ; Shimamoto, Satake et al. 1998; Lee, Jin et al. 2001; Kessler, Rappaport et al. 2003; Torlontano, Attard et al. 2004; Ito, Tomoda et al. 2005; Ito, Tomoda et al. 2006; Jeong, Baek et al. 2006; Stulak, Grant et al. 2006; Gonzalez, Cruz et al. 2007; Ahn, Lee et al. 2008; Kim, Park et al. 2008; Sugitani, Fujimoto et al. 2008; Choi, Kim et al. 2009; Roh, Park et al. 2009).
- 8 studies provided data for CT (Yoon, Kim et al. ; Lee, Jin et al. 2001; Jeong, Baek et al. 2006; Ahn, Lee et al. 2008; Kim, Park et al. 2008; Soler, Hamilton et al. 2008; Choi, Kim et al. 2009; Lee, Kang et al. 2009).
- One study involved MRI(Gross, Weissman et al. 2001) and 3 studies provided data for 18 FDG PET-CT(Yeo, Chung et al. 2001; Jeong, Baek et al. 2006; Lee, Kang et al. 2009).

5.4 Statistical Methods

There was no statistical analysis done for this review.

5.5 Results

The type of surgical procedure varied between studies. Some studies had prophylactic whilst others had therapeutic LND. The study details and validity of included studies and the validity are shown in Tables 5.1 and 5.2.

Table 5.1 Study details and validity-Central and combined (central and lateral) cervical LN

Study	Patients included	Study hypothesis	TP	TN	FP	FN	Sen	Spec	PPV	NPV	Validity of conclusion
Central											
Gross ND 2001	28	To determine the ability of MRI imaging to detect the presence of metastatic thyroid cancer in cervical LN	NA	NA	NA	NA	a	b	b	a	Invalid
Ito Y 2006	600	Investigate the clinical significance of LN in the central compartment	27	339	3	231	b	b	b	b	Valid
Sugitani I 2008	231	To prospectively analyse the outcomes of selective LND to determine when prophylactic lateral neck dissection is advisable	40	86	9	96	a	b	b	a	Invalid
Roh JL 2009[C]	133	Evaluation of preoperative US in detecting cervical LN metastases in PTC	NA	NA	NA	NA	b	b	b	b	Valid
Choi JS 2009	299	To compare the diagnostic accuracy of US, CT and combined US and CT	NA	NA	NA	NA	b	b	b	b	Valid

Kim E 2008	165	Determine the diagnostic accuracies of US, CT and combine US and CT	20	75	6	32	a	b	b	a	Invalid
Ahn JE 2008	9	Investigate the diagnostic ability of CT and US of cervical LN in thyroid cancer	NA	NA	NA	NA	a	b	b	a	Invalid
Choi YJ 2010	589	To evaluate the diagnostic accuracy of preoperative US and CT of the neck	NA	NA	NA	NA	a	b	b	a	Invalid
Soler ZM 2008	102	Investigate the ability of CT to detect subclinical nodal disease in PTC.	NA	NA	NA	NA	a	b	b	a	Invalid
Central and Lateral											
Kessler A 2003	63	The usefulness of US in diagnosing cervical LNM in PTC was investigated	14	43	0	6	a	b	b	a	Invalid
Shimamoto K 1998	77	To evaluate the usefulness of US for preoperative staging of PTC	NA	NA	NA	NA	b	b	NA	NA	Invalid
Torlontano M 2004	456	Determine the sensitivity of neck US to detect LN metastases	38	NA	NA	418	a	b	b	a	Invalid
Lee DH 2009	11	If PET-CT is more accurate than CT for detecting metastatic cervical LN in PTC	21	7	1	7	a	b	b	a	Invalid
Yeo JS 2001[C]	22	Evaluate whether FDG-PET is feasible as a pre surgical evaluation modality for I-131 scan-negative thyroid carcinoma patients	45	24	5	11	a	b	b	a	Invalid
Gonzalez	60	To determine the frequency of occult macroscopic metastasis	11	47	1	1	a	b	b	a	Invalid

HE 2007		detected by preoperative US									
Stulak JM 2006	551	Preoperative US will increase detection and assessment of the extent of LNM in PTC	NA	NA	NA	NA	a	b	b	a	Invalid

Sen-Sensitivity; Spec-specificity; PPV-positive predictive value; NPV, negative predictive value

TP-true positives; TN- true negatives; FP-false positives; FN-false negatives; NA-Not available/applicable

a incorrectly calculated

b correctly calculated

c figures available by levels, no overall figures

Table 5.2 Study Details and Validity- Lateral LN

Study	Patients included	Study hypothesis	TP	TN	FP	FN	Sen	Spec	PPV	NPV	Validity of conclusion
Ahn JE 2008	28	Investigate the diagnostic ability of CT and US of cervical LN in thyroid cancer	NA	NA	NA	NA	a	b	b	a	Invalid
Kim E 2008	165	Determine the diagnostic accuracies of US, CT and combined US and CT	20	75	6	32	a	b	b	a	Invalid
Ito Y 2005	560	Investigate the prognostic impact of lateral LMN detected by US	98	194	7	261	b	b	b	b	Valid
Sugitani I 2008	130	To prospectively analyse the outcomes of selective LND to determine when prophylactic lateral neck dissection is advisable	127	0	3	0	a	b	b	a	Invalid
Roh JL	34	Evaluation of preoperative US in detecting cervical metastases in	NA	NA	NA	NA	NA	NA	NA	NA	Invalid

2009 [c]		PTC									
Jeong HS 2006	26	To compare the diagnostics of ^{18}F-FDG PET-CT with US	14	229	5	12	a	b	b	a	Invalid
Choi YJ 2010	589	To evaluate the diagnostic accuracy of preoperative US and CT of the neck	NA	NA	NA	NA	a	b	b	a	Invalid
Lee K 2010	70	To investigate the usefulness and limits of US in PTC	199	76	1	55	a	b	b	a	Invalid
Yoon JH 2011	112	To evaluate the most accurate criteria using US and CT in predicting lateral LN in PTC	NA	NA	NA	NA	a	b	b	a	Invalid
Soler ZM 2008	102	Investigate the ability of CT to detect subclinical nodal disease in PTC.	NA	NA	NA	NA	a	b	b	a	Invalid
Choi JS 2009	53	To compare the diagnostic accuracy of US with that of CT in patients with PTC	NA	NA	NA	NA	a	b	b	a	Invalid

Sen-Sensitivity; Spec-specificity; PPV-positive predictive value; NPV, negative predictive value;

TP-true positives; TN- true negatives; FP-false positives; FN-false negatives: NA-Not available/applicable

a incorrectly calculated; b correctly calculated

c figures available by levels, no overall figures

5.5.1 USS (Table 5.3): For central LN, there were seven studies which provided the data (Mulla and Schulte 2012). Out of these, only 4 studies calculated sensitivity and NPV correctly. The mean sensitivity and NPV of these 4 studies was 38.4% and 60.9% respectively.

11 studies providing data for lateral LN detection by US were included. Of these only one (Ito, Tomoda et al. 2005) was accurate in their calculation of sensitivity and NPV. The sensitivity and NPV for this study were 27.2% and 43%, respectively. Five studies provided clustered results for both central and lateral cervical LN detection, out of which only one (Shimamoto, Satake et al. 1998) calculated the sensitivity (36.7%) correctly.

Table 5.3 Ultrasonography in detection of cervical LN in PTC (Mulla and Schulte 2012)

Study	Total Patients (n)	Sensitivity (%)	Specificity %	PPV %	NPV %
Central					
Ito Y 2006	600	10.5	99.1	90	59.5
Sugitani I 2008	231	29	91	82	47
Roh JL 2009	133	61	93	92	63
Kim E 2008	165	(38)	93	77	(70)
Ahn JE, 2008	37	(55)	69	77	(44)
Choi JS 2009	299	53	80	61	74
Choi JY 2010	589	(47.2)	94.8	90.4	(63.5)
Lateral					
Ito Y 2005	560	27.2	96.5	93.3	43
Jeong HS 2006	26	(41.3)	97.4	73.1	(90.6)
Stulak JM 2006	551	(83.5)	97.7	88.8	NA
Sugitani I 2008	361	NA	NA	98	NA
Roh JL 2009	133	NA	NA	NA	NA
Kim E 2008	165	(64)	92	83	(82)
Ahn JE 2008	37	(65)	82	86	(59)
Choi JS 2009	299	(93.9)	25	93.9	(25)
Choi JY 2010	589	(69.1)	94.8	57.6	(96.8)
†Lee K 2010	70	(78.3)	98.7	99.5	(58.2)
Yoon JH 2011	113	(74.3)	82.7	85.3	(70.5)
Combined Central and Lateral					
Shimamoto K, 1998	77	36.7	89.3	NA	NA
Kessler A 2003	63	(70)	100	100	(87.6)
Torlontano M, 2004	456	(100)	100	NA	NA
*Stulak JM 2006	219	(90.4)	78.9	93.9	NA
Gonzalez HE 2007	60	(92)	98	92	(98)

Figures in brackets indicate erroneous calculations; *Re-operated group of patients; †Unclear if all LN were dissected;

NA-not available/applicable

5.5.2 CT (Table 5.4): Eight studies provided data on CT scan for detecting cervical LN. For central LN, five provided data out of which in only one (Choi, Kim et al. 2009) the calculations were correct. The sensitivity and NPV in this study was 67% and 80% respectively.

Table 5.4 CT in the detection of cervical LN metastases in PTC (Mulla and Schulte 2012)

Study	Patients Total (n)	Sensitivity %	Specificity %	PPV %	NPV %
Central LN					
Kim E 2008	165	(50)	91	79	(74)
Soler ZM 2008	102	(58)	72	72	(58)
Ahn JE 2008	37	(74)	44	72	(47)
Choi JS 2009	299	67	79	65	80
Choi JY 2010	589	(41.9)	97.4	93.6	(65.1)
Lateral LN					
Jeong HS 2007	26	(42.3)	96.6	57.9	(93.8)
Kim E 2008	165	(74)	95	89	(86)
Soler ZM 2008	102	(50)	71	50	(63)
Ahn JE 2008	37	(78)	78	86	(68)
Choi JS 2009	299	(81.7)	100	100	(30.8)
Choi JY 2010	589	(78.2)	93.3	54.4	(97.7)

Yoon JH 2011	113	(68.6)	78.8	81.4	(65.1)
Combined Central and Lateral LN					
Lee DH 2009	11	(75)	87.5	95.9	(50)

Figures in brackets indicate erroneous calculations

Out of the seven studies included for lateral LN, none calculated the sensitivity and NPV correctly. There was one study with combined results for both central and lateral LN which again calculated inaccurately.

5.5.3 MRI (Table 5.5): We found one study by Gross N. D et. al (Gross, Weissman et al. 2001) in literature providing data for use of Magnetic Resonance Imaging in detection of cervical LN which again failed to calculate it in a correct manner.

5.5.4 18 FDG PET-CT (Table 5.5): Three studies provided results, one for lateral LN and two for combined central and lateral LN. In neither of these were the calculations correct.

Table 5.5: 18-FDG PET/CT and MRI in the detection of CLN in Papillary Thyroid Cancer.

Study	Total Patients (n)	Sensitivity %	Specificity %	PPV %	NPV %
18-F PET/CT					
Lateral					
Jeong HS 2006	27	(50)	97	65	(94.6)
Combined Central and Lateral					
*Yeo JS 2001	22	(80)	83	90	(69)
*Lee DH 2009	11	(35.7)	87.5	90.9	(28)
MRI					
Gross ND 2001	105	(95)	51	84	(78)

Legend: Figures in brackets indicate erroneous calculations

5.6 Discussion

In any cancer management, it is crucial to have accurate staging as it impacts on the treatment strategy and hence on long-term outcomes and survival. Imaging modalities are integral part of this initial assessment and staging. Accurate diagnostic evaluation can often lead to stage migration from a lower to higher stage. Stage migration will be reflected in the overall cancer specific survival rates (Chan, Lang et al. 2013). The importance of a thorough preoperative evaluation in PTC and subsequent neck dissection to an appropriate extent during initial surgery has been emphasized in many studies (Chow, Law et al. 2003; Mazzaferri 2009). As previously mentioned, cervical lymph node status at presentation affects long term outcomes (Lundgren, Hall et al. 2006).

In our systematic review, we assessed the 'usefulness' and 'diagnostic accuracy' of these imaging modalities. There are four parameters namely sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), which define the diagnostic accuracy of a test. Of these parameters sensitivity and NPV are important as these represent those cases 'NOT' missed by the test (Mulla and Schulte 2012). For any imaging modality to be widely used for cancer staging, it would be expected to score high on all the four parameters. A false high sensitivity or negative predictive value of the tests employed would lead to under-staging.

Sensitivity is the 'proportion of true positives that are correctly identified by the test'(Altman and Bland 1994). Put in plain language, it is the ability of a test to identify those patients with the disease (Lalkhen A.G 2008), defined by the formula TP/TP+FN (TP-True positives; FN- False negatives).

'NPV' is defined as the 'proportion of subjects with a negative test result who are correctly diagnosed'(Altman and Bland 1994). In other words it is the likelihood of a patient not having the disease when the test result is negative (Lalkhen A.G 2008) and is defined by the formula TN/TN+FN (TN- True Negatives).

For calculation of sensitivity and NPV, 'False negatives' (FN) values are required as is evident from the above formulae. The only practical method to obtain FN values is to dissect all cervical LN during surgery irrespective of image findings followed by comparison of histology results to those detected by pre-operative imaging. This alone will ascertain that all 'FN' cases are included. This can only be achieved by performing prophylactic lymph node dissection alone.

From our systematic review on imaging, it is evident that out of the 16 studies providing values for sensitivity and NPV of US, only 6 studies calculated these values accurately leaving 10 studies with either incomplete or inaccurate data (Table 5.3). Results from studies involving CT, only one (Choi JS 2009) out of 8 studies provided accurate results for sensitivity and NPV. The remaining 7 studies provide incorrect results (Table 7.4). The same applies to 18 FDG PET-CT and MR studies; all 4 included calculated the values incorrectly (Table 7.5). In summary, only 7 out of 28 imaging studies included have performed the calculations correctly leaving with 21 studies with incorrect calculations. In all the studies, which did not calculate the sensitivity

and NPV accurately, patients had therapeutic LND, hence 'FN' cases could not have been obtained.

When correct scientific methodology was applied, the mean sensitivity and NPV of US was 36.2% and 57.3%, respectively. The only study, which provided correct results for CT had a sensitivity of 67% and NPV of 80% for central compartment only (Choi, Kim et al. 2009).

The results from our review clearly shows that US and CT are not ideal imaging for the detection metastatic cervical LN. The discrepancies in calculating reflect a misunderstandings or simply incorrect definitions of the terms 'sensitivity' and 'NPV' in the context of imaging cervical LN in PTC.

Ultrasound is operator dependent and hence individual results may be better than what has been published in literature. There are no set diagnostic criteria for detecting metastatic cervical LN although there are suspicious features as described previously. This adds to the problem of subjectivity in detecting suspicious LN even further. However, such operator dependency puts obvious limitations to the use of the results in cancer staging and management which will affect outcomes and survival. It is clear from the above findings that properly designed studies calculating FN correctly and thereby providing accurate values for sensitivity and NPV are required to resolve this issue.

Some newer methods of evaluating metastatic cervical LN like dual-energy spectral CT and USS guided FNA thyroglobulin washout are still in their early phases and not well established (Liu, Ouyang et al. 2014; Jun, Kim et al. 2015).

The role of sentinel lymph node (SLN) biopsy in PTC has been investigated and debated for a long time. The aim of this is to identify cervical LN metastasis without performing a formal LN dissection thus in theory avoiding unnecessary operations. It relies on the progression of metastases in an orderly fashion from the primary organ to the sentinel LN or groups of LN's. Several methods have been used in the detection of SLN in PTC namely methylene blue, radio-isotope and combination of techniques(Balasubramanian and Harrison 2011). This method has not gained popularity for a variety of reasons. Dye spillage during injection causes problems with identification of SLN in addition to causing difficulty in defining other groups of LN. Lymphatic disruption during dissection and blockage of the lymph channels with

tumour can lead to non-visualisation of the SLN (Abdalla 2006; Peparini, Maturo et al. 2006). False identification of SLN for stained parathyroids can lead to excision of these glands (Lee, Choi et al. 2009). Rigorous studies are needed to establish this technique to be used in management of PTC.

5.7 Limitations

1. The review was not registered in accordance with PRISMA guidelines on databases such as PROSPERO.
2. The quality of the included studies has not been assessed.

Chapter 6

Multicentre Retrospective Cohort Study

6.1 Aims and Objectives

1. To compare the outcomes between prophylactic lateral cervical LN dissection versus no lateral LND.
2. To determine the extent of lateral cervical LN metastasis after prophylactic lateral LN Dissection.

6.2 Methods and Methodology

Study period was 9 years from 2004-2012.

We conducted a retrospective study at two large hospitals in London namely

- King's College Hospital (KCH)
- Guy's and St. Thomas' Hospital (GSTT)

A comprehensive list of all patients treated for PTC was obtained in liaison with the histopathology department from the above centres. All patients had undergone surgery for PTC. All available information and data was collected from individual patient case notes, Electronic Patient Records (EPR), radiology reporting system, histopathology reporting system, letters from Thyroid Multidisciplinary team (MDT) meetings and nuclear medicine department. Histological classification was done according to World Health Organisation (WHO) classification of thyroid tumours (Hedinger 1989). Staging was done according to TNM classification (7th Edition) of thyroid cancer (Sobin L 2002). The data was collected in accordance with the National and regional guidelines of these trusts. Ethical approval was sought and was deemed not necessary by the ethics committee. All data was anonymised and stored in a password protected hard drive and on an encrypted USB.

The data collected included:

- Demographics
- Pre-operative imaging
- Type of surgical procedure i.e Lobectomy, TT, LN Dissection
- Type of Lymph Node dissection whether prophylactic or therapeutic
- Extent of cervical LN dissection
- Prevalence of LN metastases in central and lateral compartment

- Recurrence and methods used for its detection
- Follow-up data was collected to the last clinic letter
- Outcomes of surgery relating to recurrence and survival.

Management regimes at the two centres

The surgical management of thyroid cancer at the two centres differed mainly for tumours T3 and above. Patients from King's College Hospital with tumours pT3 and above, were likely to have prophylactic MRND although this was found not to be consistent for all patients. At the other centre, namely GSTT similar cohort of patients were likely to have lateral cervical LN dissection only if metastatic LN were detected pre-operatively on imaging or clinical examination.

It must be emphasised that it is not possible to discuss here, the individual scenarios that might have transpired or influenced the surgical management of individual cases discussed and decided in the multi-disciplinary meetings.

For our analysis, we divided the patients into two Cohorts as follows-

Cohort A (Prophylactic Lateral Cervical LND) - In this group the surgical approach was prophylactic MRND. These patients had total thyroidectomy and Modified Radical Neck Dissection along with central LN dissection. This group included only those patients who did NOT have any suspicious or metastatic lateral LN on clinical examination, imaging and intra-operatively.

Prophylactic MRND was defined as type III MRND with removal of cervical LN from levels II to V irrespective of pre-operative/intra-operative findings or pre-operative imaging with preservation of the spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle (Sakorafas, Sampanis et al. 2010). Neck levels were defined according to the consensus statement on classification of cervical LN as defined by Robbins et. al (Robbins, Shaha et al. 2008). The surgeon removed all upper, middle, lower jugular LN including those from the posterior triangle of the neck corresponding to levels II to V.

Cohort B (Central Cervical LND)-This group of patients had total thyroidectomy and therapeutic central cervical LND. None of these patients had suspicious or confirmed lateral LN metastasis on pre-operative imaging or clinical examination.

This operative procedure involved dissection of the level VI compartment to remove pre-tracheal, para-tracheal nodes, pre-cricoid (Delphian) and the peri-thyroidal nodes along with fatty tissue and fascia.

Recurrence

Cervical LN or loco-regional recurrence was defined as evidence of LN metastases at least six months after completion of initial treatment (surgery+/-RAI treatment). Recurrence was suspected by clinical or ultrasound examination and confirmed by aspiration cytology, resection, high levels of Tg or by imaging studies, such as post I I31 treatment whole body scan or Positron Emission Tomography (PET). Histological confirmation of nodal metastases was confirmed in all cases after surgery.
In case of suspicious or metastatic cervical LN detected prior to this period of six months, this was considered as 'persistence of disease.'

6.3 Statistical Methods

All statistical analysis was performed using the software SPSS version 21 (SPSS Inc., Chicago, IL). We calculated mean, median, standard deviation and the range for the descriptive variables. For uni-variate analysis of the risk factors, chi-square values and Pearson's correlation coefficient (p-values) were calculated for comparison between the two groups. $P < 0{\cdot}05$ was considered statistically significant.
To calculate the recurrence free survival, we used Kaplan-Meier survival curves.

6.4 Results

There were 224 patients in total who had surgery for thyroid cancer in the two centres over a 9-year period. There were 51 males and 173 female patients. 74 patients belonged to KCH and 150 were treated at GSTT. The demographics and other patient characteristics are as shown in Table 6.1.

Table 6.1: Demographics and other patient characteristics of all patients

Characteristic	KCH† LND (n=74)	GSTT‡ (n=150)	Chi square/p value
Male / Female	24 / 50	27 / 123	5.9 P=0.01
Age n of patients Mean ±SD Range ±SD	 74 48.5 ±15.8 20 – 86	 150 50.0 ±15.1 22 – 88	n.s.
Focality n Uni /Multifocal	 70 40 / 29	 142 77 / 65	n.s.
Laterality n Unilateral /Bilateral	 69 49 / 20	 141 84 / 57	n.s.
Size of primary tumour n Mean ±\SD Range	 60 2.0 ±1.7 0.1 – 7.5	 125 2.2 ±1.8 0.1 – 12.5	n.s.
T Staging n T1 T2 T3 T4	 74 36 10 23 5	 150 59 42 32 17	 8.5 P <0.05
Imaging for LN USS CT MRI Any imaging	**Performed / Positive** 40/4 4/0 7/0 46/4	**Performed / Positive** 65/13 35/14 20/5 85/25	 n.s. n.s. n.s. p=0.004
Follow up (months) n	 74	 148	

Mean ± SD	31.5 ±21.8	40.4 ±22.7	7.8
Range	1.0 – 84.4	2.0 – 95.9	<0.01
Recurrence			
n	74	148	
Mean ± SD	3	10	n.s.
No recurrence	71	137	
Radio-iodine (Number of doses)			
n	70	150	
Mean ± SD	1.1 ±1.0	1.5 ±1.1	6.7
Range	0 - 4	0 - 7	P = 0.02
Radio-iodine (Total dose)			
n	48	129	n.s.
Mean ± SD	6.8 ±5.2	7.6 ±6.6	
Range	0.2 – 29.6	3.6 – 38.8	
Death			
n	74	148	
Dead	0	3	n.s.
Alive	74	145	

†-King's College Hospital

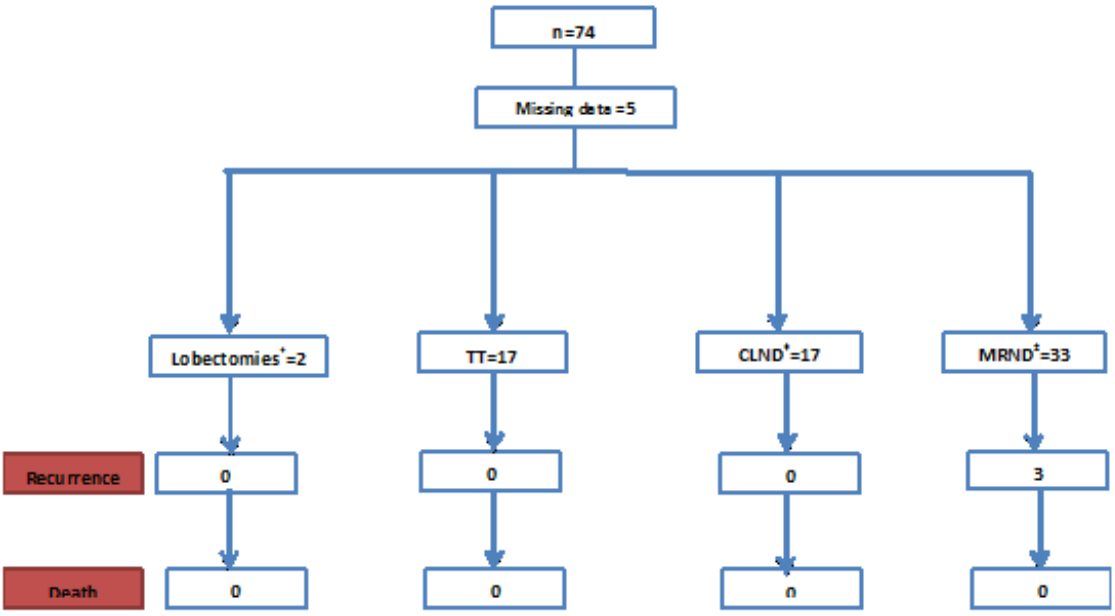
‡-Guy's and St. Thomas' Hospital

There were total of 13 recurrences, 3 in the KCH and 10 in the GSTT cohort. All 3 recurrences in the KCH cohort were loco-regional. There were no deaths in this cohort. Out the 10 recurrences in the GSTT cohort, 2 patients had both loco-regional and distant recurrence; 6 patients had locoregional recurrence only with no distant recurrence; 2 had distant recurrence with no locoregional recurrence.

There were 3 deaths in this cohort; all three patients had advanced disease (T4N1b) on presentation and had undergone LND. All developed recurrence and had RAI treatment for the same.

The flow of patients and the outcomes for all patients from KCH are as shown in Figure 6.1. The available TNM staging of all patients as per the surgical procedure performed is shown in Table 6.2.

Figure 6.1 Flow of all patients at King's College Hospital (KCH)



†-Includes Hemithyroidectomies

‡-Includes Ipsilateral and Bilateral CLND

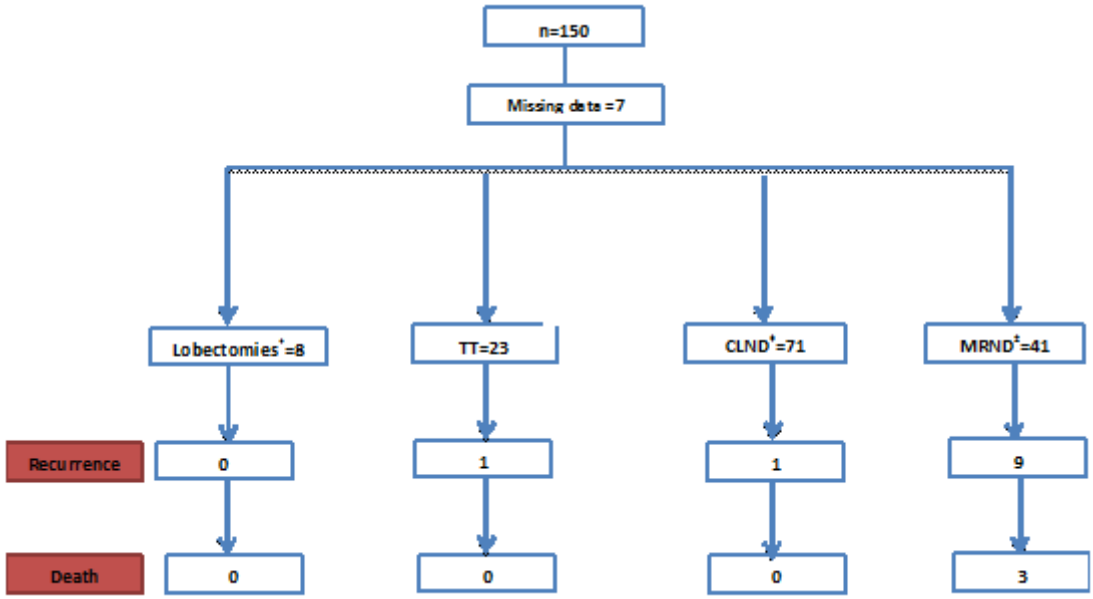
±-Includes Ipsilateral, Bilateral, prophylactic and therapeutic LLND

Table 6.2: Tumour Staging (TNM) and the surgical procedure performed at King's College Hospital

Stages	Lobectomy n=2	TT n=17	CLND n=17	LLND n=33
T1	1	13	9	12
T2	0	3	1	5
T3	1	1	6	12
T4	0	0	1	4
Nx	0	6	0	1
N0	0	6	11	5
N1	0	0	1	2
N1a	0	0	0	3
N1b	1	0	0	17
Missing Data	1	5	5	5
Mx	1	7	5	22
M0	0	3	1	0
M1	0	0	1	2
Missing Data	1	7	10	9

Similarly, the flow of patients and the outcomes for all patients from Guy's and St. Thomas' hospitals (GSTT) are as shown in Figure 6.2.

Figure 6.2 Flow of all patients at Guy's and St. Thomas' (GSTT) Hospitals



†-Includes Hemithyroidectomies

‡-Includes Ipsilateral and Bilateral CLND

±-Includes Ipsilateral, Bilateral LLND and selective compartmental LND

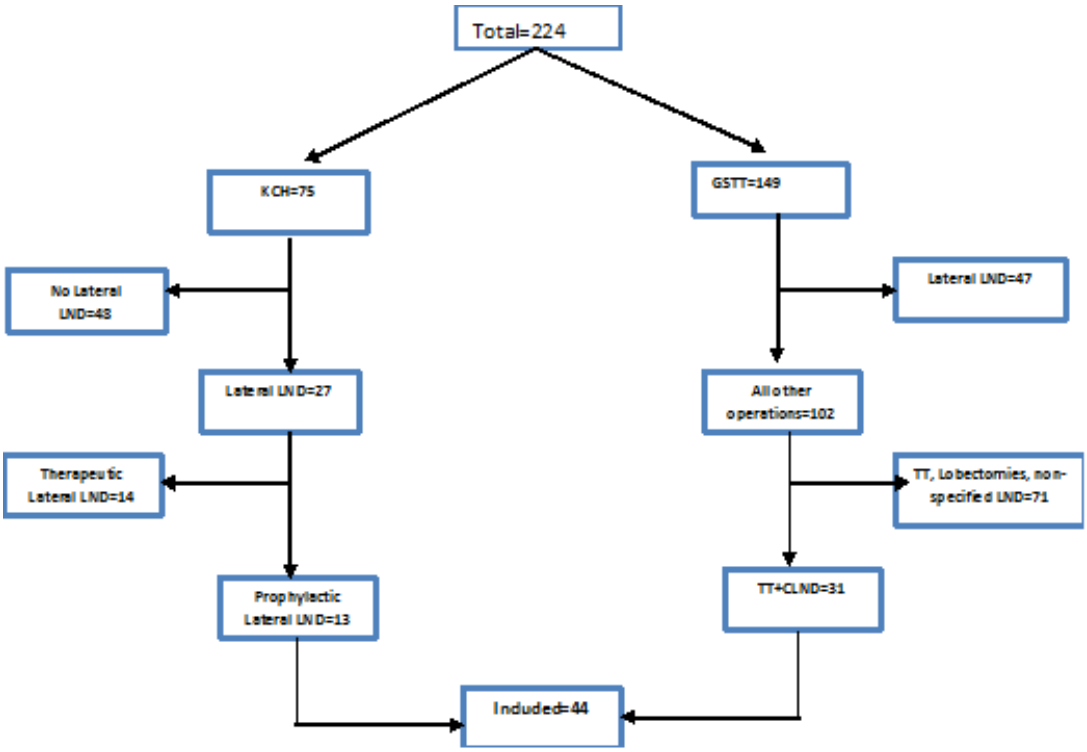
The available TNM staging of all patients from GSTT as per the surgical procedure performed is shown in Table 6.3.

Table 6.3 Tumour Staging (TNM) and the surgical procedure performed at GSTT

Stages	Lobectomy n=8	TT n=23	CLND n=71	LLND n=41
T1	4	16	30	8
T2	3	2	25	9
T3	1	4	12	13
T4	0	1	4	11
Nx	2	3	7	0
N0	2	13	36	2
N1	0	0	2	0
N1a	0	0	10	4
N1b	0	1	2	32
Missing Data	4	6	14	3
Mx	1	7	25	11
M0	1	4	19	13
M1	0	0	1	0
Missing Data	6	12	26	17

Results of Analysis of the two Cohorts

Figure 6.3 shows the flow of patients and the process of inclusion in the two cohorts.



Total of 44 patients fulfilled the above inclusion and exclusion criteria and hence were included in the analysis. 31 patients had TT and central LND whilst 13 patients had TT+CLND prophylactic lateral LND. There were 10 males and 34 female patients with a mean age of 43.3 years. The median follow-up period was 28 months (Range: 1-96 months). Of the 13 patients who had prophylactic lateral LND, 7 (53.8%) were found to have positive LN on histology**.** Among the central LND group, out of 31 patients 9 (29%) were found to have positive LN. Uni-variate analyses between gender, tumour size and focality did not show any significant difference among the two groups (Table 6.4). Patients undergoing central LND were older and there was a significant difference in the ages between the two cohorts ($p<0.01$).

Table 6.4 Demographics and Uni-variate analyses of risk factors for the two Cohorts

Risk Factor	Prophylactic Lateral LND n=13	Central LND n=31	Chi square (p value)	All Patients
Gender				
Male/female	5/8	5/26	n.s	10/34
Age (years)				
n of patients	13	31		44
Mean ± SD	36.5±9.5	50±15.3	8.7	46.0±15.3
Median	35	47.0	(<0.01)	45.0
Range	20-53	26-85		20-85
Size of primary tumour (cm)				
n of patients	11	28		39
Mean ± SD	2.8±1.4	2.4±1.6		2.4±1.5
Median	2.5	2.1	n.s	2.2
Range	1.1-5.5	0.1-7.0		0.1-7.0
Focality				
n of patients	13	29	n.s	24/18
Unifocal/Multifocal	7/6	17/12		
Total LN Removed	**Lateral LN**	**Central LN**		
n of patients	13	29		24
Mean± SD	23.9±13.5	7.5±6.9	27.4	12.6±12.1
Median	20	5.0	(<.0001)	14
Range	4-50	0-26		0-50
Total LN Positive	**Lateral LN**	**Central LN**		
n of patients	13	29		42
Mean± SD	1.5±1.8	1.1±2.1	n.s	1.1±2.1
Median	1	0		1
Range	0-5	0-8		0-8

Follow-up (Months)				
n of patients	13	31		44
Mean± SD	24.2±15.2	41.7±24.1	5.8	36.5±23.2
Median	23.3	35.9	(<0.05)	28
Range	1-54	2-96		1-96

n: number of patients with available data
n.s: not statistically significant
LN: lymph nodes

Table 6.5 Results of Central Lymph Nodes Dissection-part of LLND from the KCH Cohort

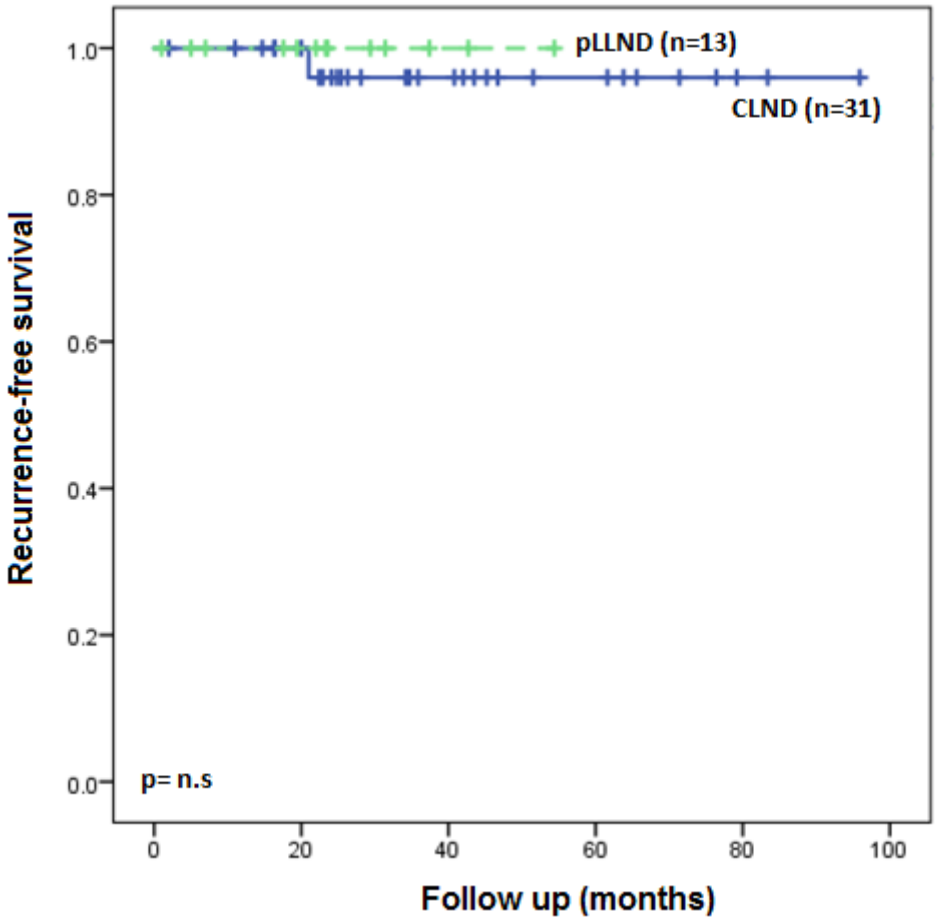
Total LN removed	
n	13
Mean± SD	7.7±9.6
Median	4
Range	0-34
Total LN Positive	
n of patients	13
Mean± SD	1.1±1.7
Median	0
Range	0-5

n- Number of patients with available data

LN-lymph nodes

There were no recurrences in the prophylactic group whilst there was one recurrence in the CLND group. Kaplan-Meir analysis showed that recurrence free survival was not significant between the two groups (Fig. 6.4).

Figure 6.4 Recurrence free survival in between the two cohorts



Results of Radio-iodine treatment

The mean dose of Radio-iodine (RAI) in the prophylactic lateral LND and central LND groups was 5.0 GBq (SD±2.8) and 6.0 GBq (SD±5.5) respectively. This was not statistically significant. The mean number of RAI doses in the prophylactic lateral LND and central LND groups was 1.2 (SD±0.7) and 1.2 (SD±1.0) respectively. The difference also was not statistically significant (Table 6.6).

Table 6.6 Radio-iodine (RAI) treatment between the two groups

RAI	Prophylactic	Therapeutic	Chi square (p value)	All patients
Radio-iodine number of doses				
n	12	31		43
Mean±SD	1.2±0.7	1.2±1.0	n.s	1.2±0.9
Median	1.0	1.0		1
Range	0-3	0-5		0-5
Radio-iodine dose (GBq)				
n	11	25		36
Mean ±SD	5.0±2.8	6.0±5.5	n.s	5.6±4.8
Median	3.8	3.9		3.9
Range	1.1-11.6	3.6-27		1.1-27.0

n-number of patients with available data

n.s: not statistically significant

6.5 Discussion

For decades, there has been considerable controversy regarding the type of surgical approach and the extent of lateral cervical lymph node dissection in PTC. This debate is compounded by lack of data on long term outcomes and survival.

In this study, more than half of patients who underwent pLLND had metastatic lateral LN. We have also shown from previous systematic review that lateral cervical

LN metastases were found in nearly 50% of patients when prophylactic LND was performed (Mulla, Knoefel et al. 2012). Other studies have shown that more than half of PTC patients with metastatic central LN also had metastatic lateral LN (Hartl, Leboulleux et al. 2012).

There was only one recurrence in central LND cohort and no recurrences in the pLLND group. Kaplan Meir analysis showed 'recurrence free survival' between the two cohorts not to be significant.

We could not perform any meaningful analysis of known risk factors for recurrence of disease as there was only one recurrence in the two cohorts combined. We also could not perform five or 10-year recurrence free survival because of very small of patients in the data with long enough follow-up period for any meaningful statistical analysis. There were no deaths in either cohort; hence overall 'Overall Survival' was 100%.

The pros and cons of prophylactic lateral LND have been discussed in the preceding chapters. Although lateral LN metastasis appears to be quite common, their significance in relation to long-term outcomes is not very clear. The main reason for this is the lack of long term follow-up data required to obtain any meaningful results. In an ideal scenario, data from randomised controlled trials with long term follow-up would be required to assess long term outcomes. For a slow growing tumour such as PTC, it is difficult to organise RCT as this would need long term follow-up to achieve any meaningful statistical significance (Shaha 2004). The feasibility of conducting a prospective randomized controlled trial comparing prophylactic central node dissection versus no prophylactic central node dissection for cN0 PTC has been analyzed by a multidisciplinary subcommittee of the ATA Surgical Affairs Committee (Carling, Carty et al. 2012). They concluded that 'given the low rates of both newly identified structural disease, prohibitively large sample sizes would be required for sufficient statistical power to demonstrate significant differences in outcomes' (Carling, Carty et al. 2012). 'Thus, a prospective RCT of prophylactic central lymph node dissection in cN0 PTC was not readily feasible' (Carling, Carty et al. 2012).

Out of the studies providing long term data, some have shown that cervical LN metastases were related to a higher recurrence rate, but did not adversely influence survival (Hay, Grant et al. 1992). Other authors have documented that the presence

of lymph node metastases adversely influenced disease free and overall survival (Scheumann, Gimm et al. 1994; Ito, Higashiyama et al. 2007). There is evidence in literature from large studies and reviews confirming that lateral cervical involvement (II-V) has poor survival and an increased risk of death from PTC (Smith, Sessions et al. 2012; Eskander, Merdad et al. 2013). In our study the because of small number of patients and short follow-up period, (Median=28 months) it was not possible to draw any meaningful long term conclusions.

There are also studies from large registries like SEER (Surveillance, Epidemiology, and End Results) database from United States of America. One such study demonstrated lymph node status to be an independent predictor of survival in PTC patients >45years of age but did not affect survival in <45 years (Zaydfudim, Feurer et al. 2008). A similar recent SEER based study with nearly 26,000 PTC patients demonstrated a significant association between lymph node involvement and cumulative incidence of death from thyroid cancer (P<0.001). There are other studies which show that cervical LN metastases were related to a higher recurrence rate, but did not adversely influence survival (Hay, Grant et al. 1992). Others have reported that the presence of lymph node metastases adversely influenced survival (Scheumann, Gimm et al. 1994). A study by Ito Y and colleagues demonstrated that clinically identified lymph node metastases are associated with a worse disease free and overall survival (Noguchi, Murakami et al. 1998; Ito and Miyauchi 2007). A recent study of a large series of more than 11,000 PTC patients concluded that patients aged >45 years with lateral/mediastinal cervical involvement have an increased risk of death from PTC (Smith, Sessions et al. 2012). These studies however do not provide a comparison between prophylactic and therapeutic LND in PTC.

There are few studies comparing prophylactic to therapeutic LND with regards to long term outcomes. One such is a study conducted by Barczynski and colleagues (Barczynski, Konturek et al. 2013) who looked at central LN only. This was a retrospective cohort study of patients who underwent total thyroidectomy (TT) with bilateral prophylactic CND (n=358) compared with patients who had TT without CND (n=282). The 10-year disease-specific survival rate for patients who had TT without CND was 92·5% compared with 98% in patients with CND (*P* = 0·034), and the loco-regional control rate was 87·6 and 94·5% respectively (*P* = 0·003). They concluded

that bilateral pCND, improved both 10-year disease-specific survival and loco-regional control, without increasing the risk of permanent morbidity.
A recent study with cohort similar to our analysis was performed by Lim YC and colleagues (Lim, Liu et al. 2016). They studied all patients who underwent TT+CLND without any clinical evidence of lateral LN involvement; the study found lateral LN recurrence in 4.5% of patients. Tumour size >1 cm and central LN metastasis were independent predictors of lateral LN recurrence.

6.6 Limitations of Cohort Study

-As this was a retrospective study, it had significant deficiencies.
-Collection of data was reliant on the availability of complete histology reports, accurate imaging reports, operative notes and follow-up data. This was found to be significantly deficient on all the above parameters in-spite of our best efforts to gather all the data.
-There was a lot of variability in terms of information provided on the histology reports. This meant that all the required information could not be collected consistently and there was a lot of missing data.
-Some of the imaging reports were also not available. This again meant missing data which could not be collected.
-The median follow-up period for the prophylactic groups was less than 2 years. This obviously has an impact on the results and outcomes.

6.7 Summary of Conclusions

- Prophylactic lymph node dissection yielded metastatic central and lateral lymph nodes in about half of all patients with Papillary Thyroid Carcinoma. Frequency of cervical LN metastasis increases proportionately with the stage of disease.
- Imaging modalities currently utilised for detection of both central and lateral metastatic cervical LN namely US and CT have low sensitivities and hence not entirely reliable in detecting metastatic cervical LN.
- There was no difference in the clinical outcomes between prophylactic lateral LND versus no lateral LND in our study. This must be viewed within limitations of the study with small numbers involved and the short follow-up.
- A randomised controlled trial comparing prophylactic versus therapeutic LND would be necessary to provide any meaningful results on long term outcomes.

Summary of Publications

1. Central cervical lymph node metastasis in papillary thyroid cancer: a systematic review of imaging-guided and prophylactic removal of the Central compartment. Mulla M, Schulte KM. *Clinical Endocrinology (2012); 76: 131-36.*

2. Lateral cervical lymph node metastasis in papillary thyroid cancer: a systematic review of imaging-guided and prophylactic removal of the lateral compartment. Mulla M, Knoefel WT, Gilbert J, McGregor A and Schulte KM. *Clinical Endocrinology (2012); 77: 126-31.*

3. Terminology inaccuracies in the interpretation of imaging results in detection of cervical lymph node metastases in papillary thyroid cancer. Mulla M, Schulte KM. *Endocrine Connections (2012) 1(2):78-86*

Book Chapter

Book-Thyroid Cancer: Diagnosis, Treatment and Prognosis.

Chapter: Papillary Thyroid Cancer-The problem of regional LN metastases- Chapter ID 11135. **Mulla M**, Schulte KM

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